The human hippocampus in Alzheimer's disease

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E P H E

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Cyceron PLATEFORME D'IMAGERIE BIOMÉDICALE

CHUCaen

The hippocampus in Alzheimer's disease (AD)

1) Introduction: epidemiology, neuropathology and clinical diagnosis
2) Neuroimaging techniques and new criteria
3) Profile of atrophy in AD: from regions-of-interest to voxelwise analyses
4) A differential effect of AD on hippocampal subfields
5) Hippocampal circuitry and connectivity
6) Beyond the hippocampus: hippocampal networks

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Alzheimer's disease

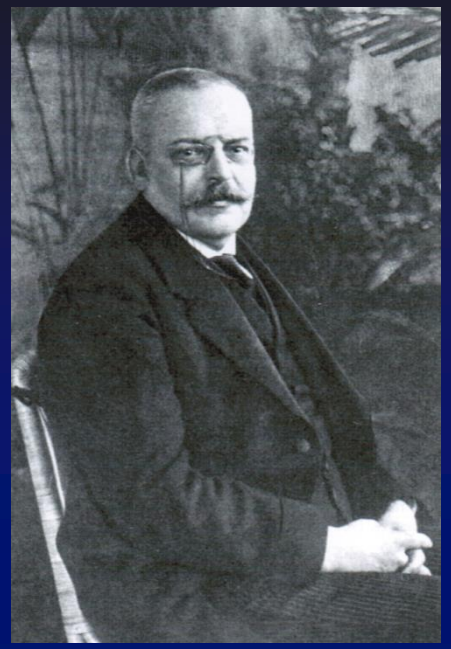
- 1st cause of dementia: 1st cause of institutionnalisation, age= main risk factor
  → exponential increase of prevalence with age

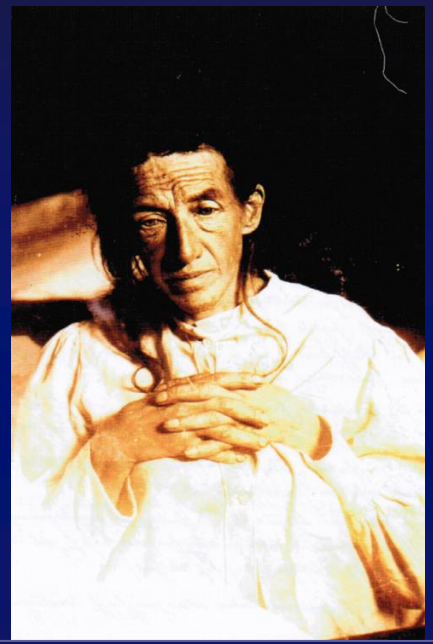
- 54% estimated increase in the number of cases in 20 years;

- The total medical (10%) and medico-social (90%) cost in France was estimated to exceed 10 billion euros in 2005 (>>> costs induced by cancer or cerebro-vascular disease) + psychological burden for the patients and their family

- No available curative treatment (and symptomatic treatments not reimbursed anymore)

Alois Alzheimer (1906)





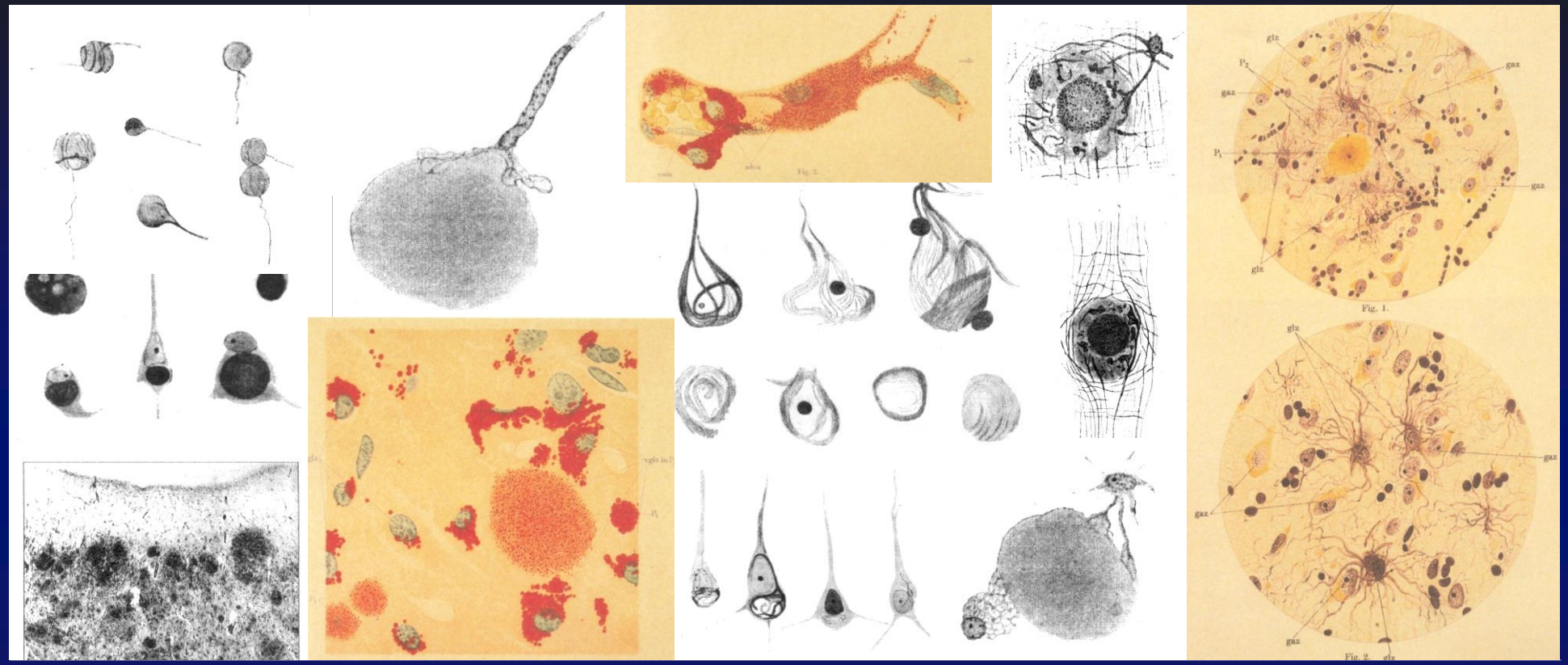
The physician who described the first case with AD = Auguste D

*Pictures: Alzheimer: **100 years** and beyond. M. Jucker, K. Beyreuther, C. Haass, R Nitsch and Y. Christen (eds.) , 2006, Berlin; Heidelberg; New York: Springer*

The clinical signs and their evolution

« […] she started to have difficulty in remembering things. Two months later, she started making mistakes in preparing meals, paced nervously and without reason in the apartment, and was not careful with the household money. She progressively became worse. […] »

Alois Alzheimer (1906)

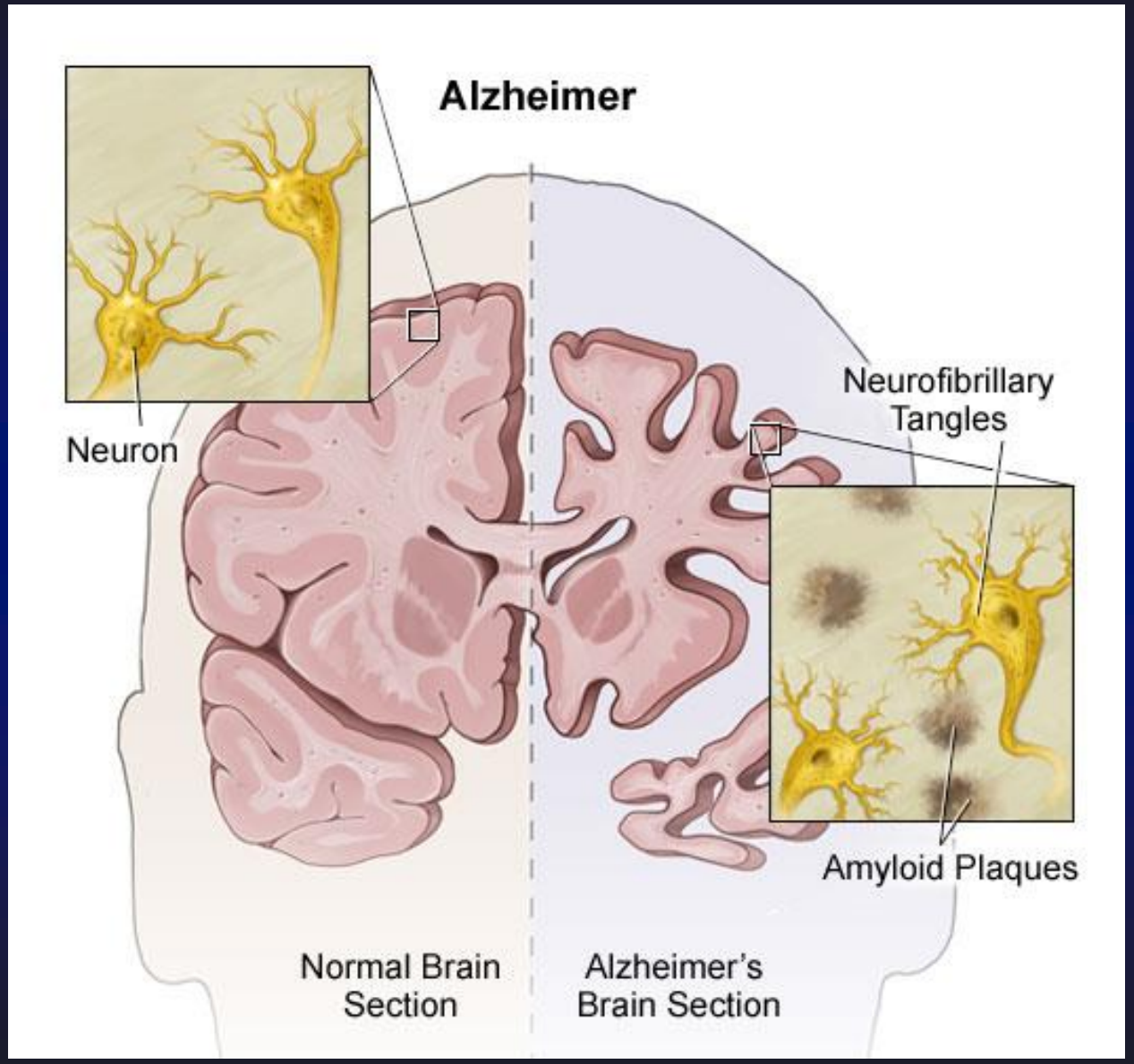


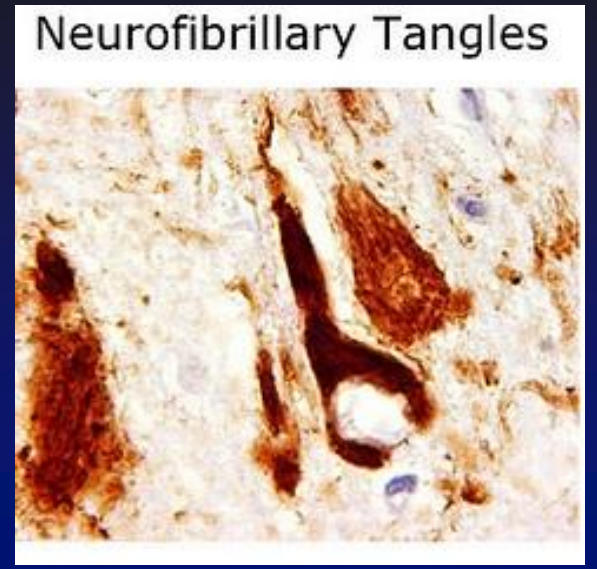
*Pictures: Alzheimer: **100 years** and beyond. M. Jucker, K. Beyreuther, C. Haass, R Nitsch and Y. Christen (eds.) , 2006, Berlin; Heidelberg; New York: Springer*

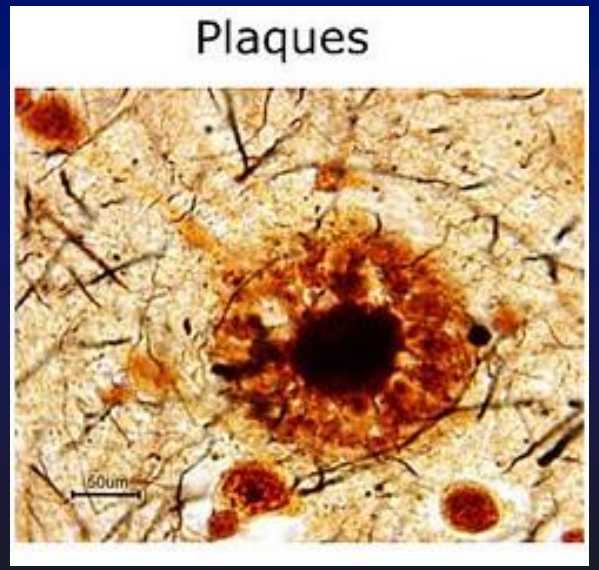
The Neuropathology

*« The autopsy showed a uniformly **atrophic** brain without any macroscopic focal abnomalities. […] In the centre of an otherwise almost normal cell there stands out one or several **fibrils** due to their characteristic thickness and peculiar impregnability. Numerous small miliary foci [**amyloid plaques**] are found in the superior layers. They are determined by the storage of a peculiar material in the cortex. All in all we have to face a peculiar disease process [which has] been verified recently in large numbers. »*

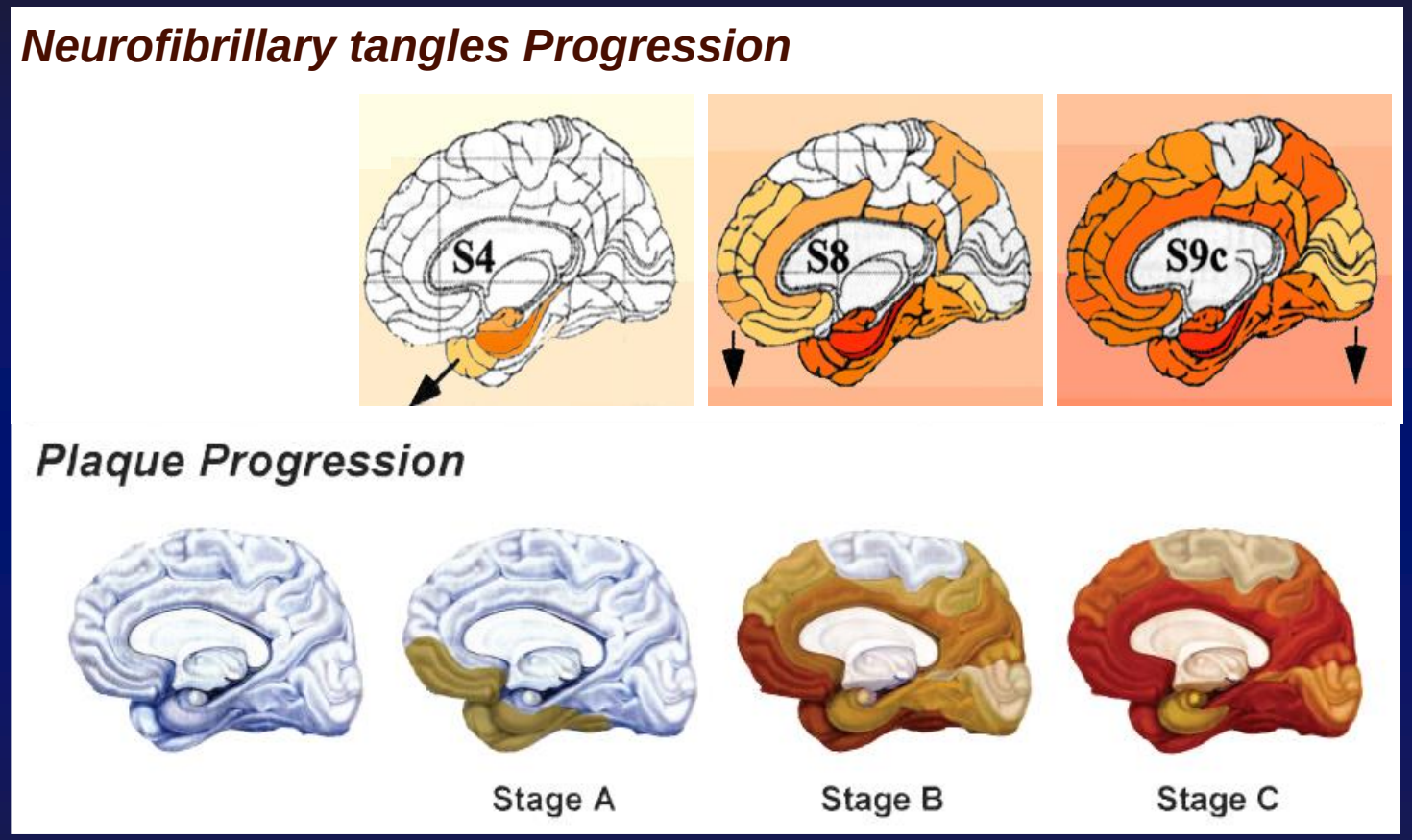
NEUROPATHOLOGY







TANGLES AND PLAQUES



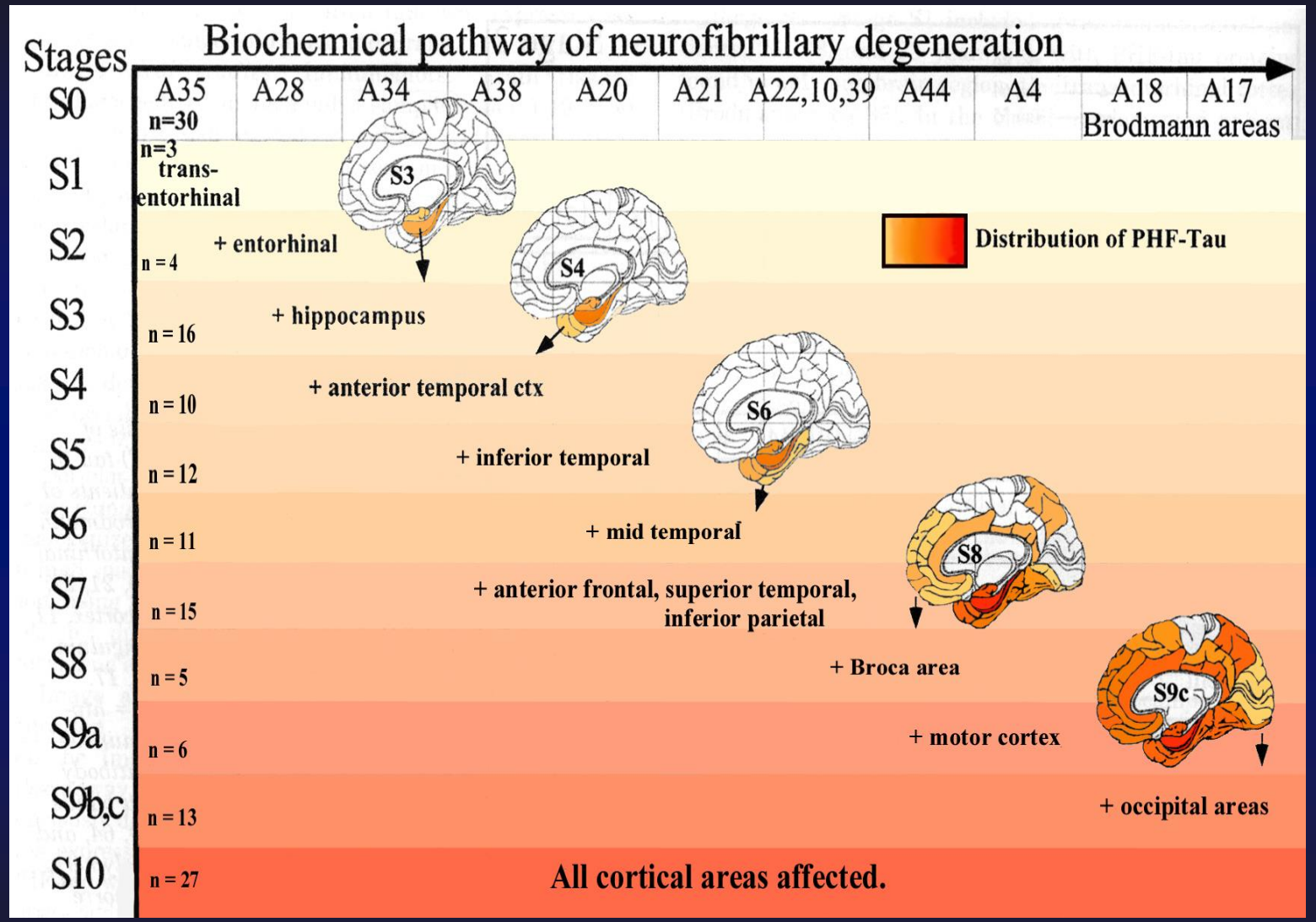
1) Entorhinal – Hippocampal area ;
2) Temporal;
3) Frontal;
5) All associative neocortex
6) Primary cortex and cerebellum

1) Neocortex ;
2) Entorhinal – Hippocampal area ;
3) Subcortical nuclei ;
4) Brainstem ;
5) Cerebellum

Already present at the asymptomatic stage: Aβ deposition starts accumulating 20-30 years before the clinical manifestation of dementia

From Thal et al., Braak & Braak, Duyckaerts et al., Delacourte et al., Price et al.

NEUROPATHOLOGY: neurofibrillary tangles



Asymptomatic elderly

Isolated memory deficits (MCI)

Alzheimer's disease (Dementia)

From Delacourte et al., Duyckaerts et al; Braak and Braak

Charles Duyckaerts

Alzheimer's Disease and Neuroanatomy: Hypothesis and Proposals

C. Duyckaerts, P. Delaère, and *J.-J. Hauw*

F. Boller et al. (Eds.)
Heterogeneity of Alzheimer's Disease
© Springer-Verlag Berlin Heidelberg 1992

"We believe that the progressive involvement of the cortex occurring in Alzheimer's disease is peculiar to this disorder and is a clue to its understanding. Moreover, this progression of the disease process contrasts with the limited involvement of the brain in so-called normal aging (Hauw et al., 1988)."

"Alzheimer's disease knows something about neuroanatomy"

Charles Duyckaerts

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"Alzheimer's disease knows something about neuroanatomy"

- Neuritic plaques **preferentially target layer III** of the cerebral neocortex, which is involved in **cortico-cortical connections**.
- Tangles target **select neuronal types** (middle-size, poorly myelinated projection neurons with a long and thin axon such as pyramidal neurons) **while by-passing others** that resist the pathology (heavily myelinated projection neurons, local circuit neurons, short axon projection cells/small neurons such as granule cells) (See also Del Tredici & Braak*).

PRE-DEMENTIA STAGE

Asymptomatic stage

Subjective Cognitive Decline (SCD)

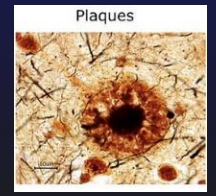
Amnestic Mild cognitive impairment (MCI)

Clinical diagnosis

Deficits of memory (episodic) + other cognitive function(s) + *impact on daily functioning*

Alzheimer's disease DEMENTIA STAGE

Neuropathological diagnosis



DIAGNOSIS CRITERIA

NINCDS-ADRDA (Mc Khann et al., 1984) / DSMV:

Probable AD: Presence of **multiple cognitive deficits (gradual and progressive change)**, one of which being **memory impairment** and the other(s) being a*phasia*, *apraxia*, *agnosia* or deficits in *executive functioning*. The deficits must **affect daily activities** (social and occupational functioning)

Post-mortem diagnosis: presence of **amyloid deposition**, **neurofibrillary tangles** and **neuronal loss** in specific brain areas

→ **Proposition of new criteria since 2008** (cf next slides)

La démence = ***trouble neurocognitif majeur*** dans le DSM-5:

Déclin cognitif qui compromet l'indépendance de la personne.
Les symptômes varient selon les types de démence dont le plus fréquent est la maladie d'Alzheimer.

Clinical presentation

Other neurological and psychiatric etiologies

Definite AD

Neuropathological features

Clinically healthy individuals

'atypical' clinical presentations

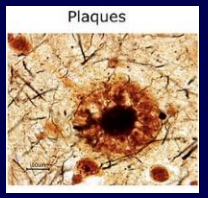
Meta-analysis from Knopman *et al.*, 2001:
probable AD : Se = 81% ; Sp= 70%
possible AD : Se= 93% ; Sp= 48%

Critères diagnostiques cliniques (NINCDS-ADRDA, Mc Khann et al., **1984**)

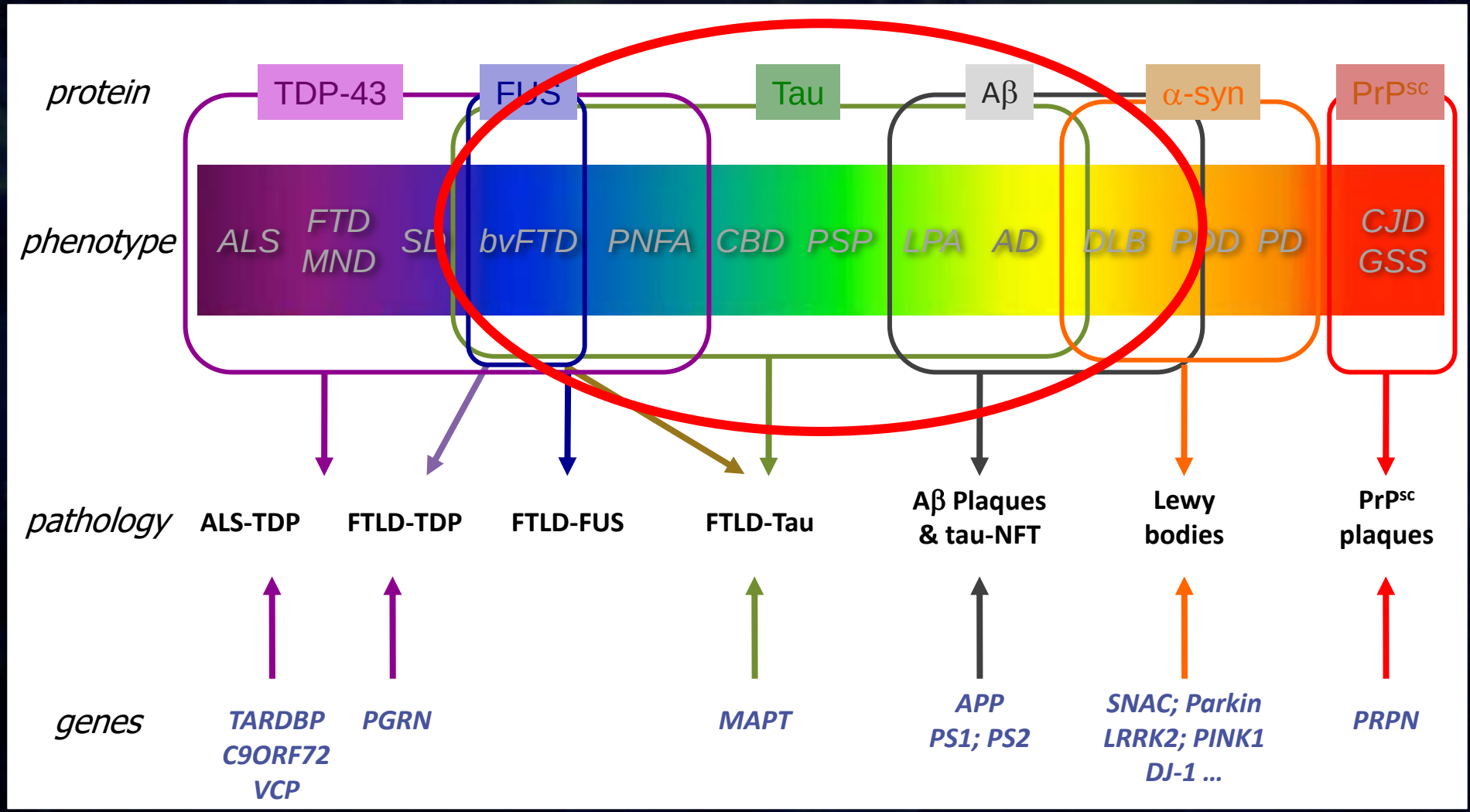
Déficit de mémoire (épisodique)
+ d'une autre fonction cognitive
+ *impact sur les activités quotidiennes*

Maladie d'Alzheimer
STADE DEMENTIEL

Diagnostic neuropathologique



Clinical, genetic and pathological spectrum of proteinopathies



Villemagne et al., Lancet Neurol 2015

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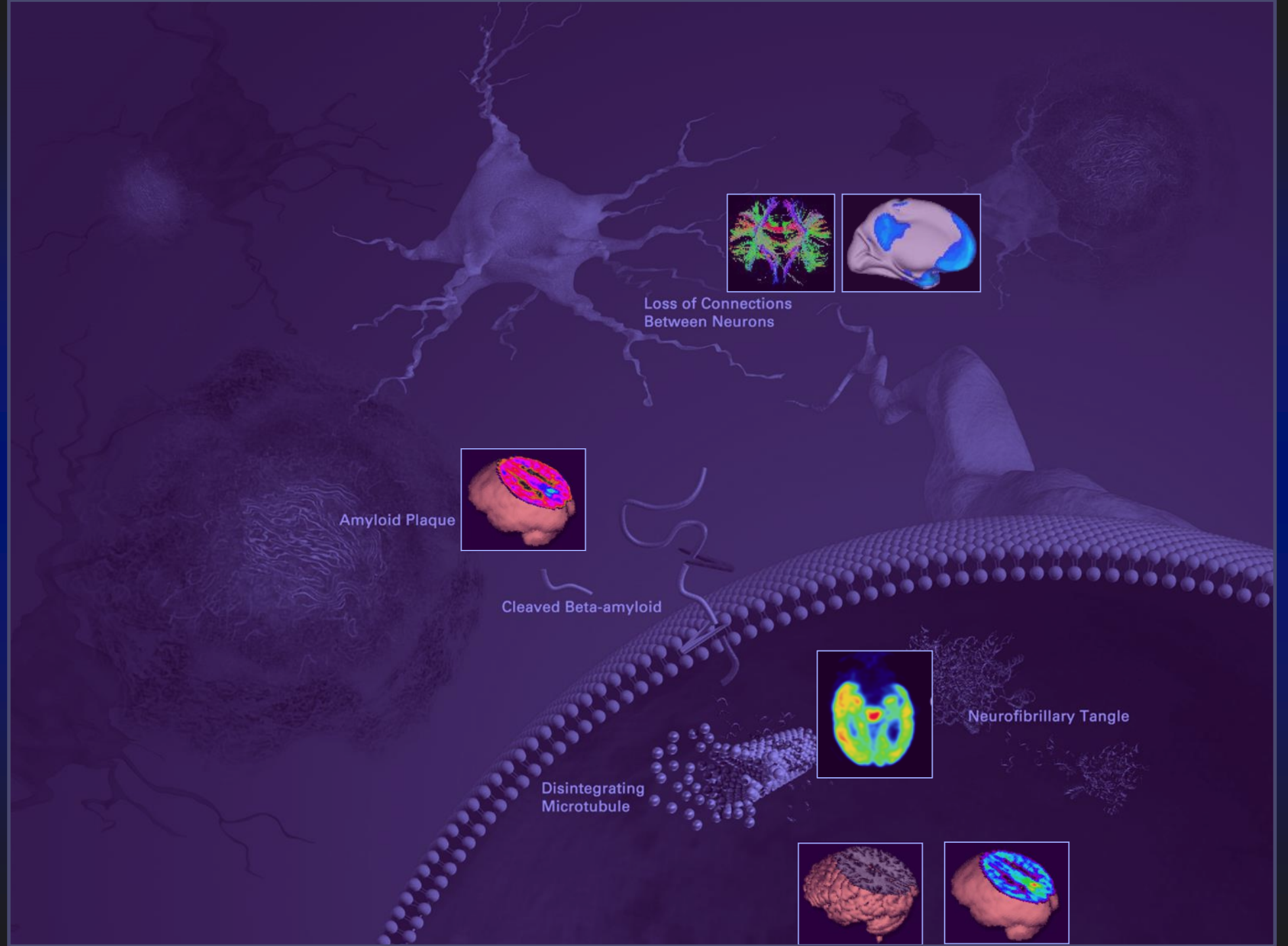
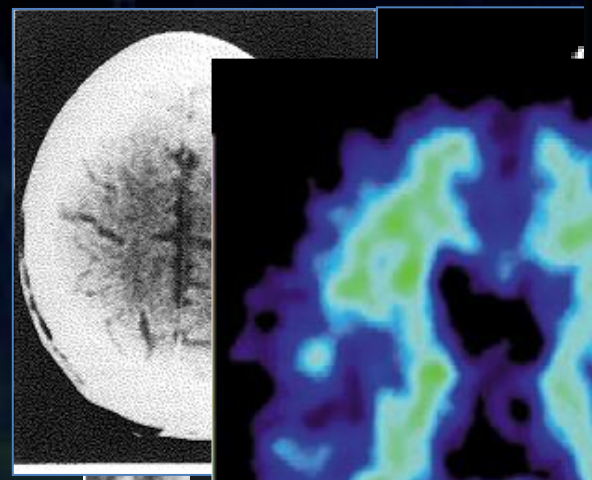
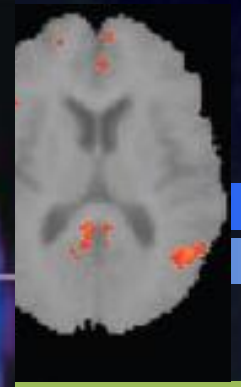

Loss of Connections
Between Neurons
Amyloid Plaque
Cleaved Beta-amyloid
Neurofibrillary Tangle
Disintegrating
Microtubule





Tau

^{18}F-Aβ

Resting-state fMRI

ole-brain voxelwise anayses

t

MRI: whole-brain voxelwise anayses

1906 1970 19 2000 2010 2020

CSF biomarkers (Aβ, tau, NFL, …

Blood biomarkers

CLINICAL CRITERIA
(McKhann et al 1984)

FROM CLINICAL TO BIOLOGICAL CRITERIA

NEW CRITERIA

AD biomarkers

Cerebro-Spinal Fluid

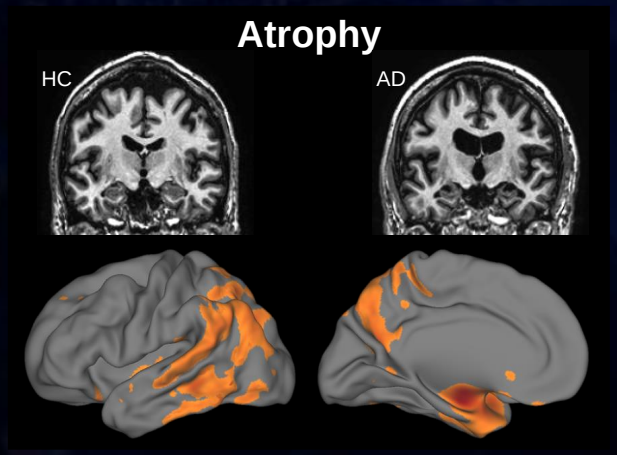
Neuroimaging

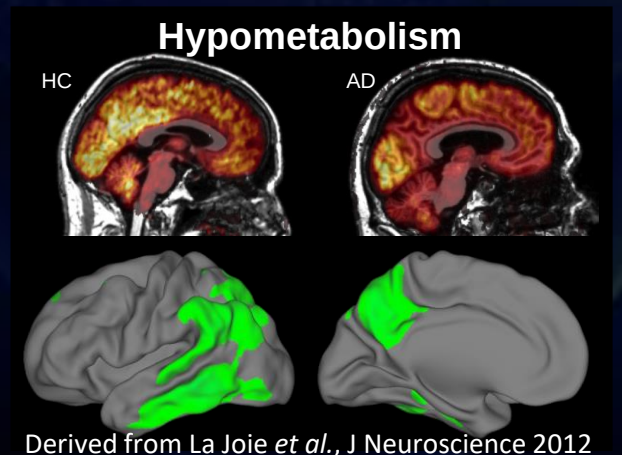
MRI

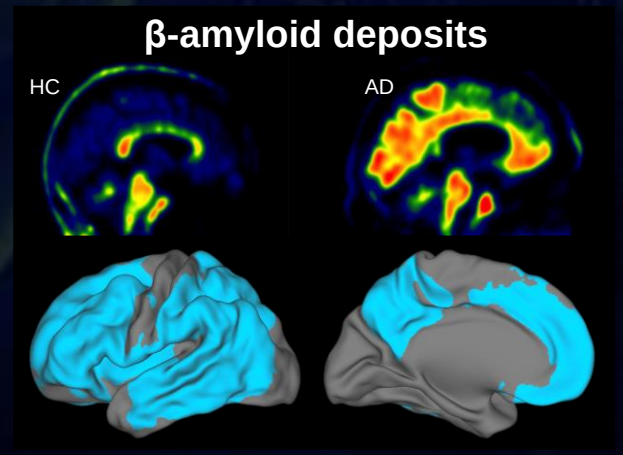
- Structural
  - T1
  - FLAIR
  - Diffusion (DTI)
- functional
  - Perfusion (ASL)
  - Resting-state

PET-scan

- Metabolism (FDG)
- β-amyloid (PIB, Florbetapir…)
- Synaptic receptors, Inflammation, …

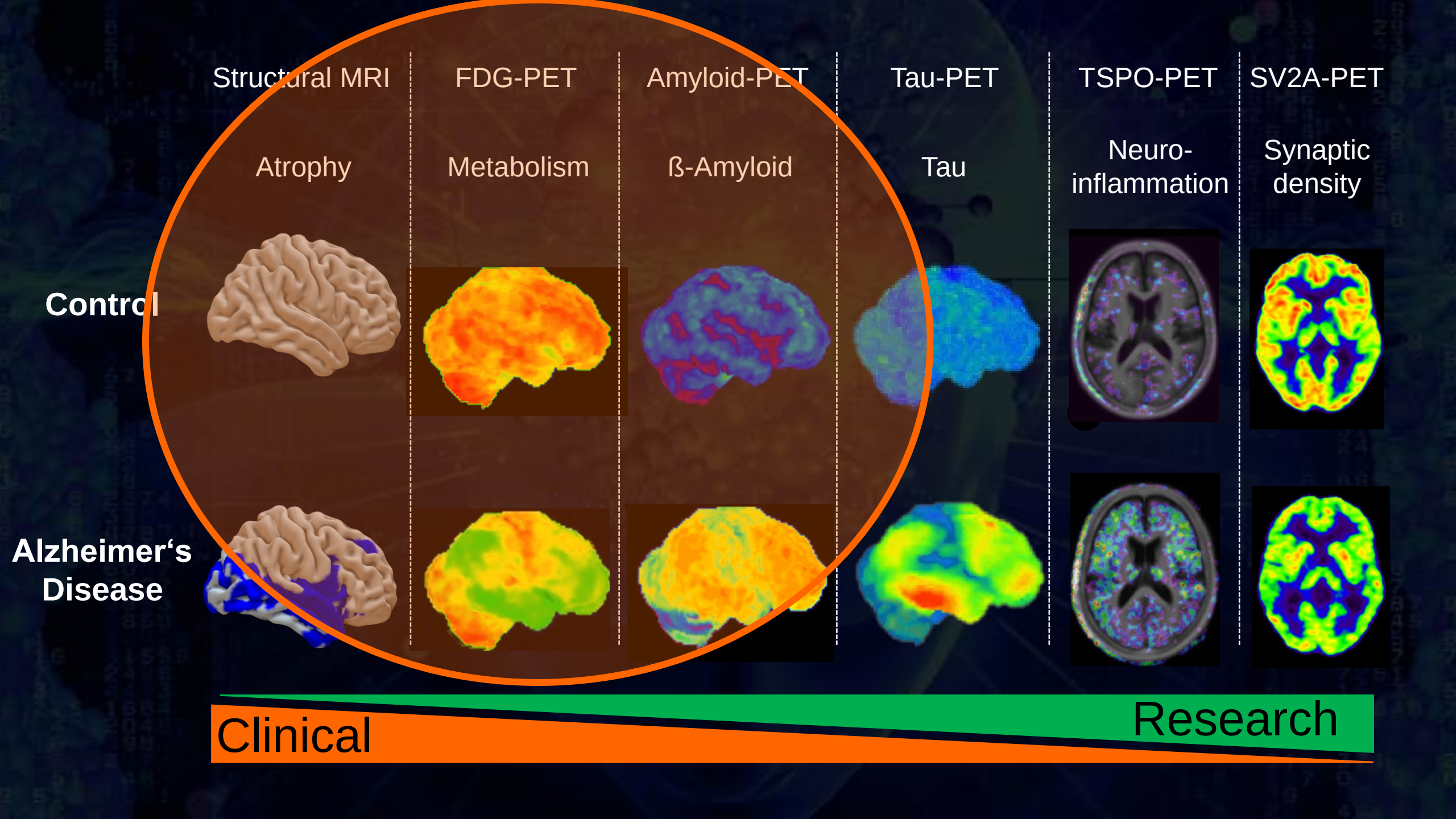




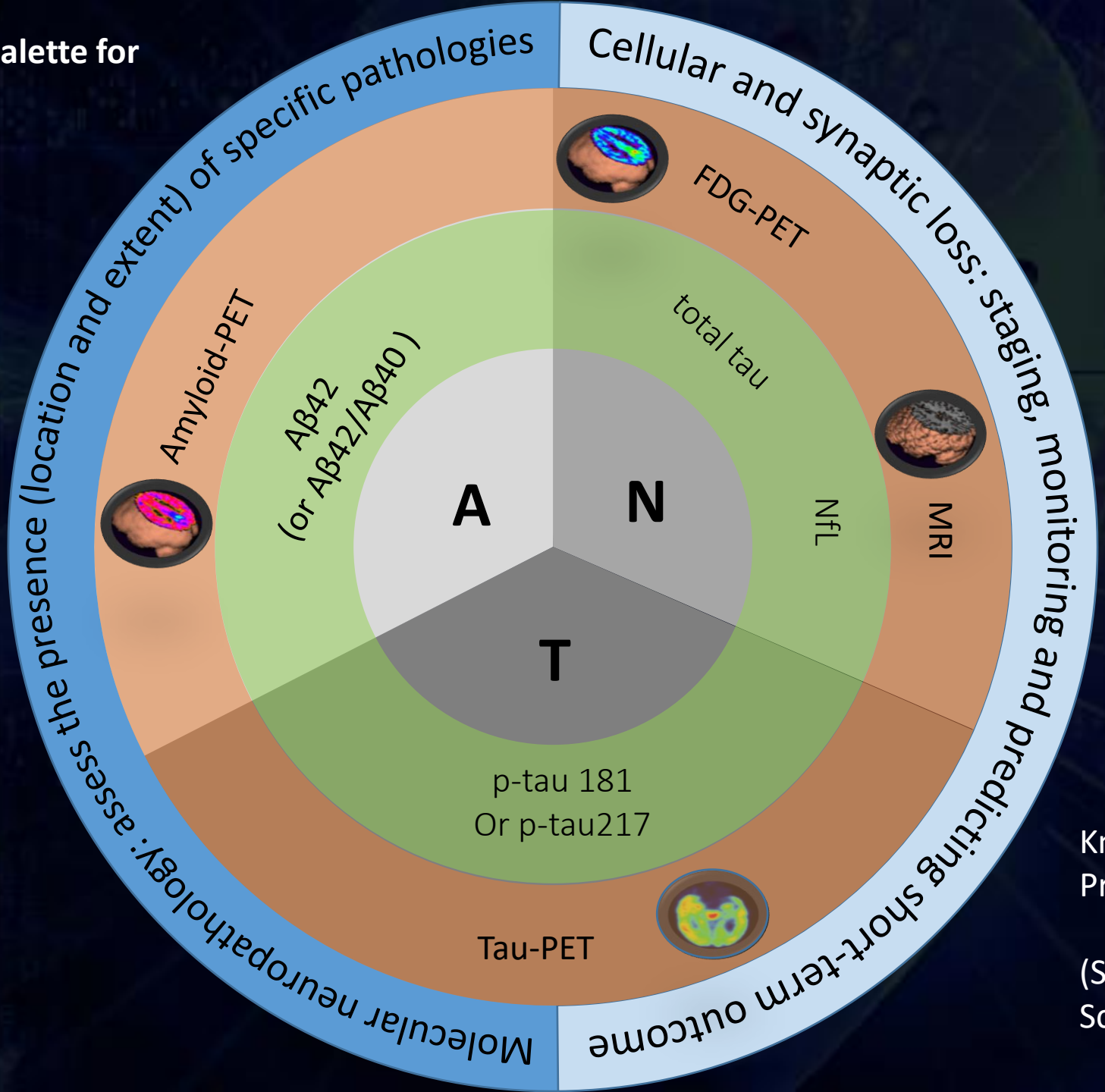


Derived from La Joie *et al.*, J Neuroscience 2012

The neuroimaging biomarker palette


Structural MRI
FDG-PET
Amyloid-PET
Tau-PET
TSPO-PET
SV2A-PET
Atrophy
Metabolism
ß-Amyloid
Tau
Neuro-inflammation
Synaptic density
Control
Alzheimer‘s Disease
Clinical
Research

The biomarker palette for AD



A/T/(N) biomarker

CSF biomarkers

Neuroimaging biomarkers

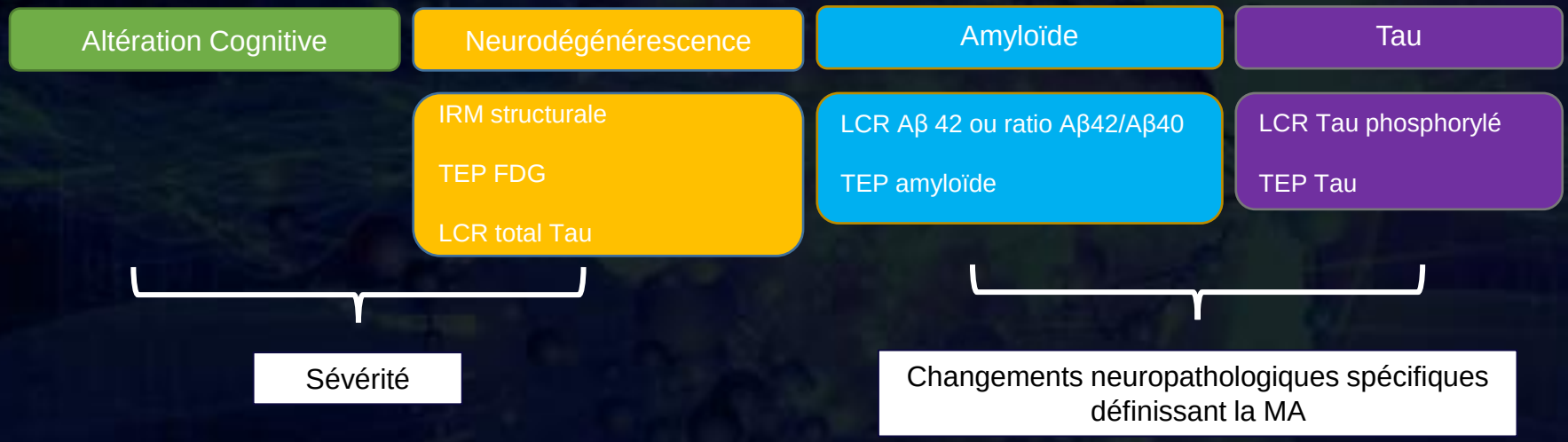
Used for

Knopman et al. Nat Rev Dis Primers. 2021

(See also Scheltens et al., Lancet. 2021)

Utilisation des biomarqueurs

(Dubois et al., 2007, 2010, 2014, 2016 ; McKhann et al., 2011; Albert et al., 2011; Sperling et al., 2011; Jack et al., 2018)



(N) **A** **T**

RESEARCH DIAGNOSTIC CRITERIA

2018 NIA-AA guidelines for research (Jack *et al., 2018 Alz Dem*)

Biomarker profiles and categories

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

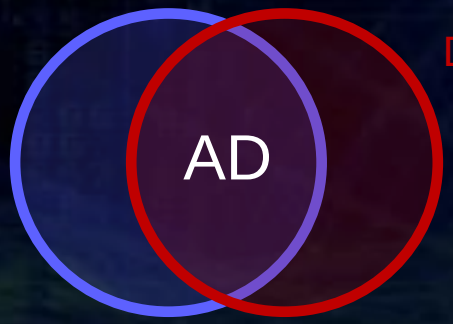
Amyloid characterizes the **Alzheimer continuum.**

Tau + Amyloid characterize **Alzheimer disease.**

- Amyloid defines the AD-pathway/continuum.
- Pathologic tau determines is someone in the AD continuum has AD (since both are required for diagnosis of the disease)
- Neurodeg/injury biomarkers and cognitive symptoms : used only to **stage severity**.

35 years of AD nomenclature and biomarker grouping (courtesy of Renaud La Joie)

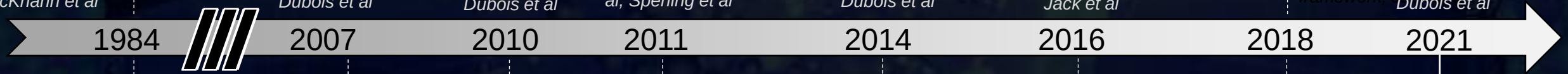
Post mortem evidence for Pathology (Aβ + tau)



AD is a **clinic-pathological entity (at autopsy)**

In vivo biomarkers of Pathology (Aβ + tau)

AD is a **pathological process** identified *in vivo* **with biomarkers**, agnostic of the presence & nature of **clinical symptoms**



NINCDS-ADRDA McKhann et al

IWG Dubois et al

IWG Dubois et al

NIA-AA clinical & research criteria: McKhann et al, Albert et al, Sperling et al

IWG-2 Dubois et al

Jack et al

NIA-AA Research framework, Jack et al

IWG recommendations Dubois et al

Biomarkers (EEG, MRI, PET, CSF, blood) are only considered to **rule out other pathologies**

3 categories of biomarkers are **incorporated to support AD Dx in research studies:** MTL atrophy | CSF | PET

2 biomarker categories
- **Pathophysiological** Aβ, tau
- **Topographical** MRI, FDG

Biomarkers **evidence for AD pathophysiological changes**, which **supports that AD underlies symptoms** and **define preclinical AD**
- **Aβ** CSF, PET
- **Neurodegeneration** CSF-Ptau, CSF-Ttau, MRI, FDG

Distinction between biomarkers:
- "**Diagnostic"/Pathology** Aβ, tau
- **Progression** MRI, FDG

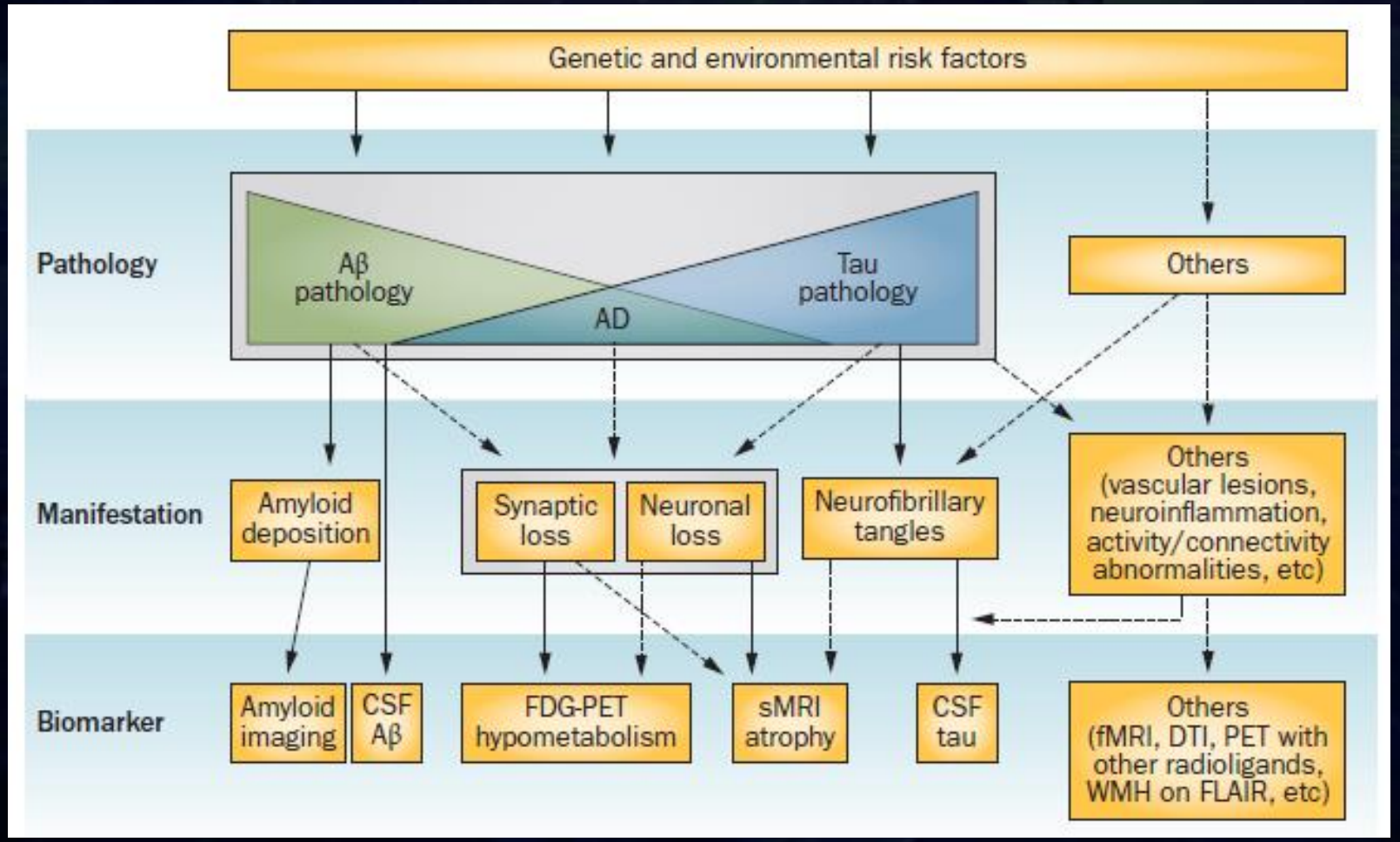
ATN scheme
- **Amyloid** CSF-Aβ, Aβ-PET
- **Tau** CSF-Ptau, tau-PET
- **Neurodegeneration** CSF-Ttau, MRI, FDG

1) Clinical-biological diagnosis
2) Common AD phenotype: A+T+= AD
3) Personalized risk profile and risk stratification

Adapted AT(N) scheme
A+ defines 'Alzheimer's continuum'
A+T+ defines AD
(N) (or Cognition) only for staging

Adapted from Leonardo Iaccarino, PhD

Neuronal injury could be caused by different factors (with various possible sequences): Aβ and tau patholgies may be partly independent, each under the influence of common and independent risk factors, and interacting with each others to promote the AD neuropathological cascade



Chételat, Nat Rev Neurol, 2013

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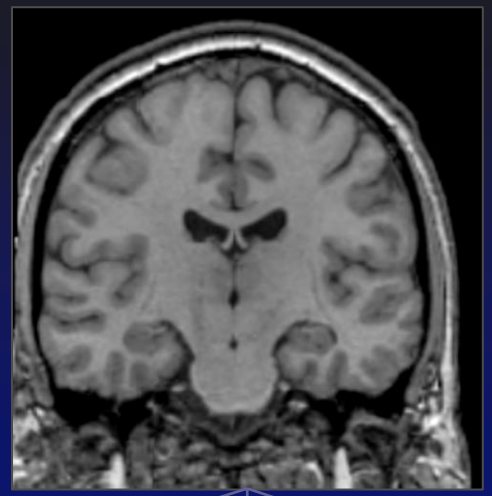
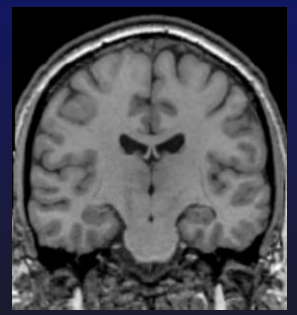
ACQUISITION

Structural MRI (T1-weighted)

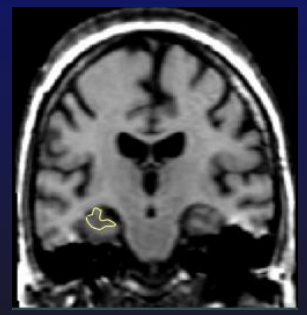


PROCESSING AND ANALYSIS

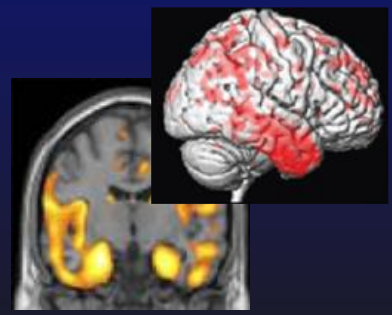
Visual



Delineation (manual or automatic) of regions of interest



Whole brain techniques



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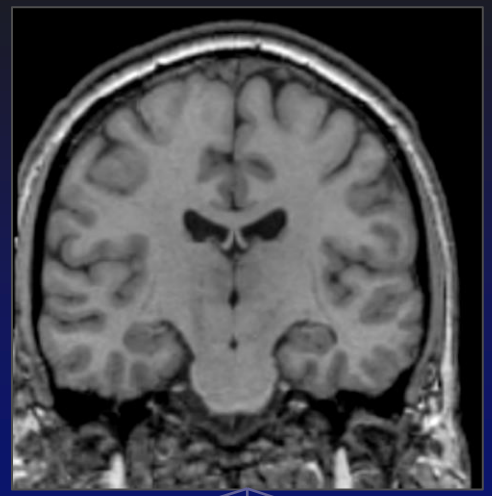

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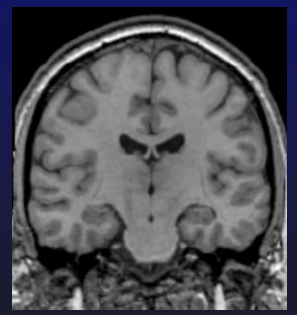

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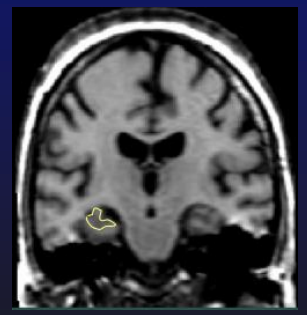

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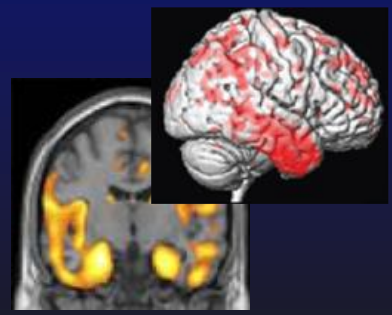


Visual rating scales (MTL)

Scheltens et al. J Neurol Neurosurg Psychiatry1992; 55:967-972

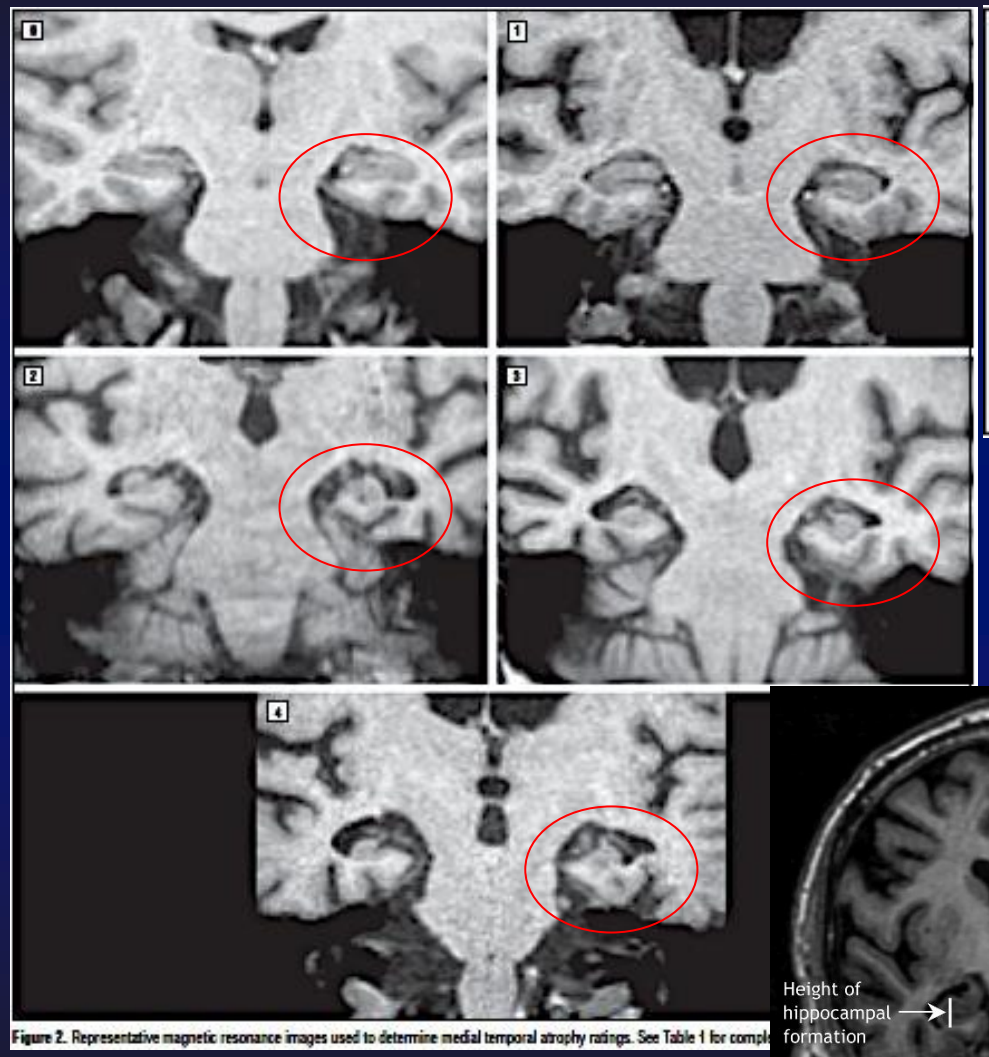
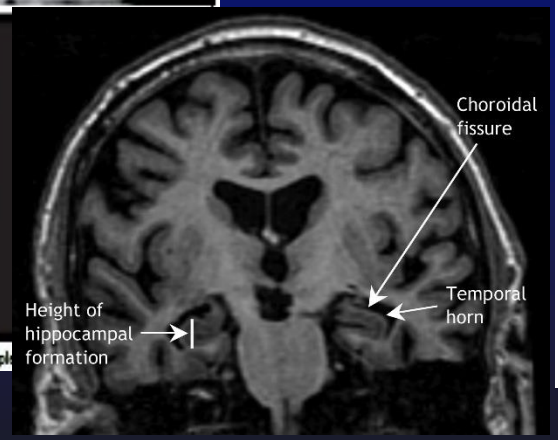


Figure 2. Representative magnetic resonance images used to determine medial temporal atrophy ratings. See Table 1 for compl

Table 1. Medial Temporal Atrophy Rating Algorithm

Score	Width of Choroidal Fissure	Width of Temporal Horn	Height of Hippocampus
0	Normal	Normal	Normal
1	Mildly widened	Normal	Normal
2	Moderately widened	Mildly widened	Mildly reduced
3	Markedly widened	Moderately widened	Moderately reduced
4	Markedly widened	Markedly widened	Markedly reduced



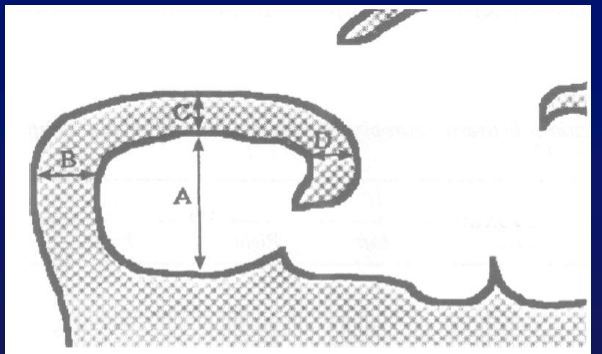
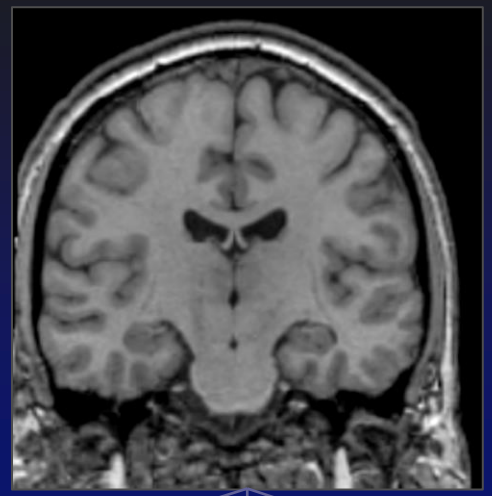


Figure 3 Schematic drawing showing linear measures of medial temporal lobe. A = largest vertical height of hippocampal formation, defined as dentate gyrus, hippocampus proper, and subiculum together with parahippocampal gyrus; B = largest horizontal width between hippocampal formation and brainstem; C = largest vertical width of choroid fissure; D = width of temporal horn.

De Carli et al. Arch Neurol 2007; 64:108-115

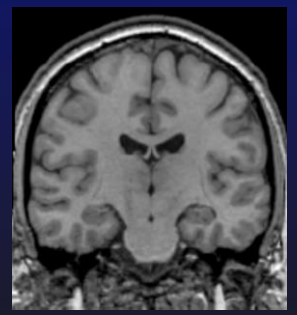
ACQUISITION

Structural MRI (T1-weighted)

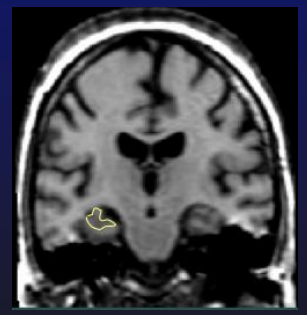


PROCESSING AND ANALYSIS

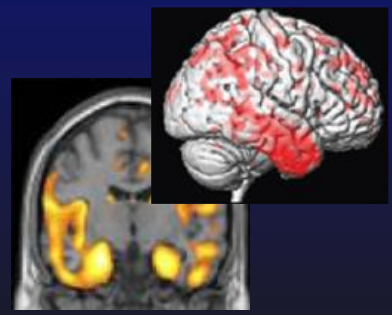
Visual



Delineation (manual or automatic) of regions of interest

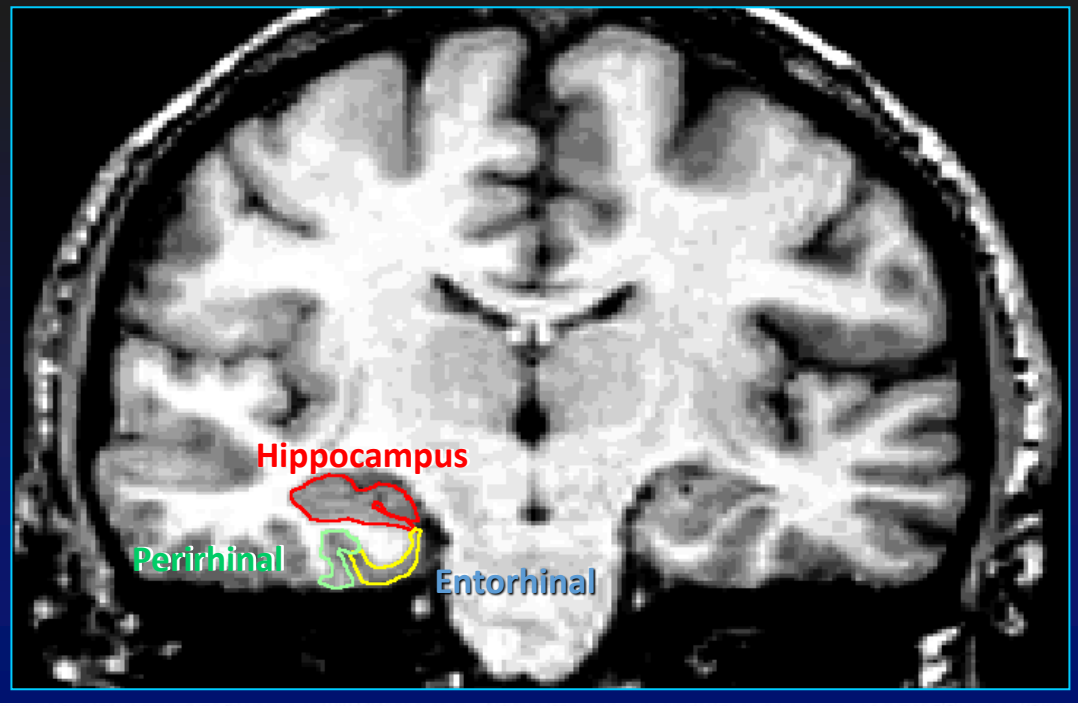


Whole brain techniques



Region-of-interest analyses

Manual delineation



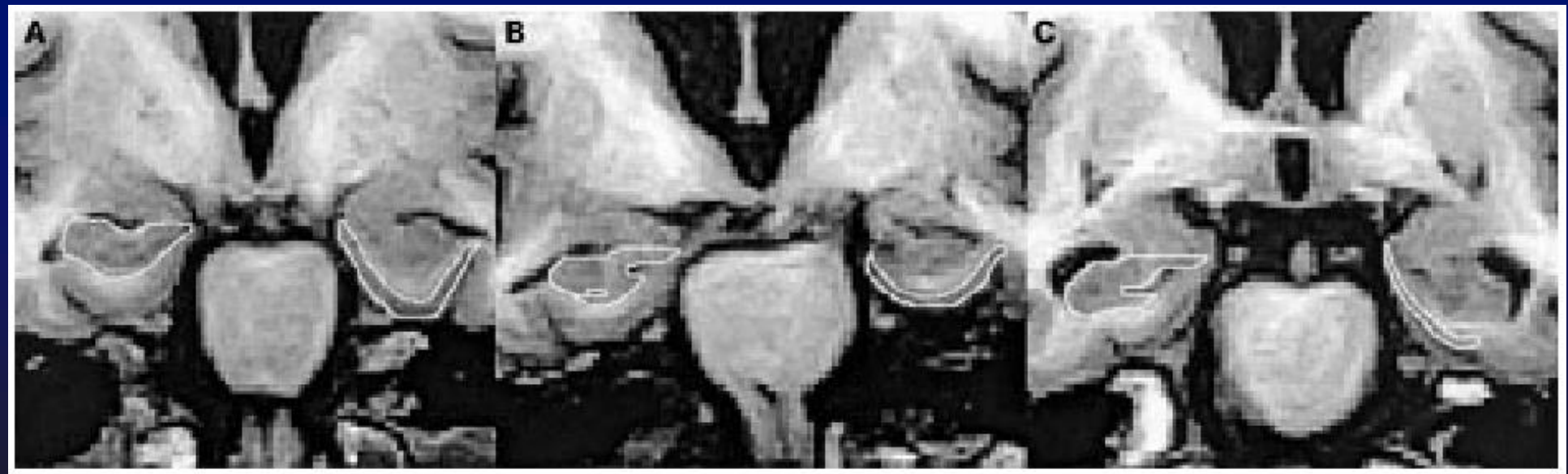
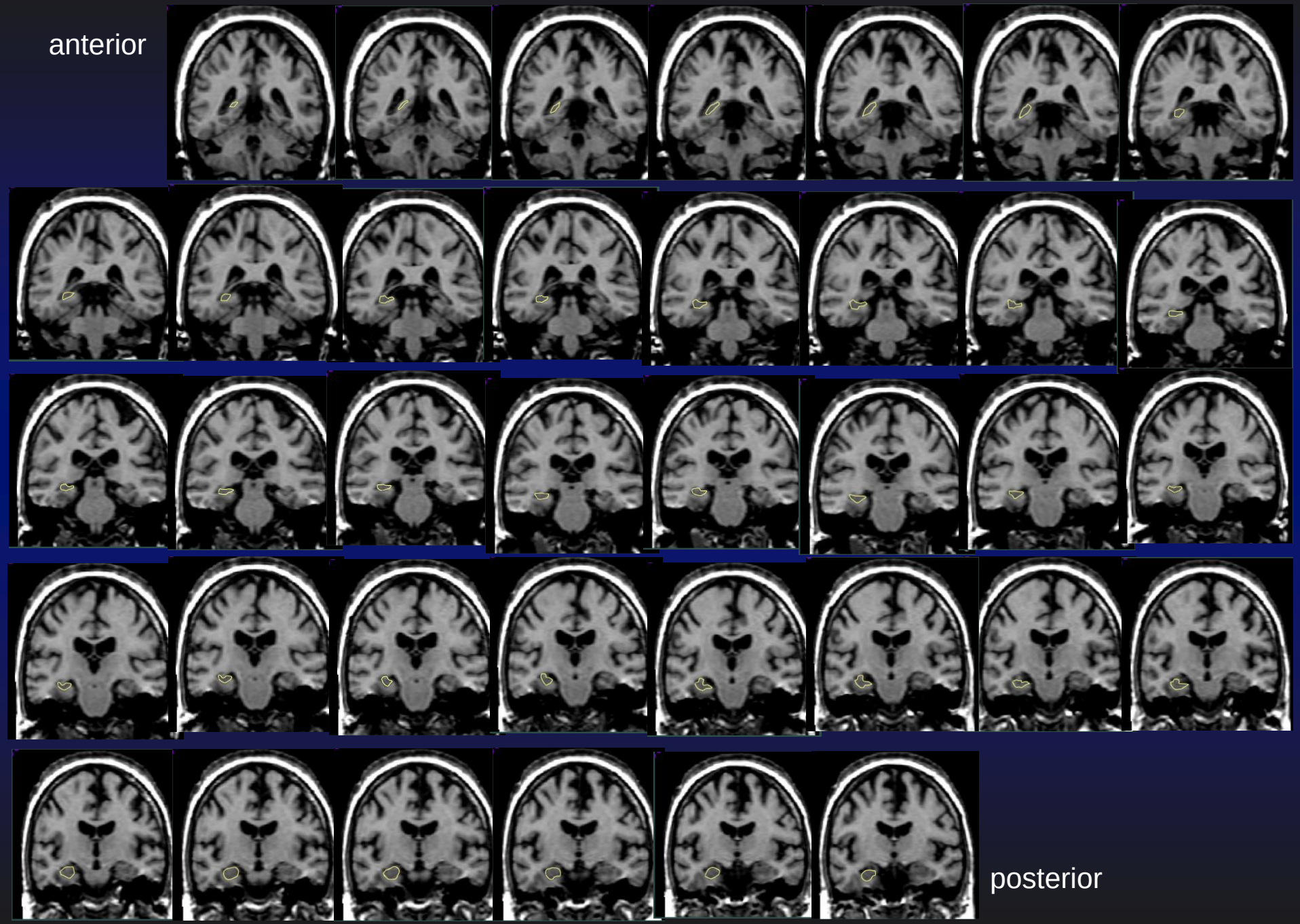


Figure 1 Entorhinal cortex (ERC) (right) and hippocampal (left) volume measurement in MP-RAGE images. (A) Normal cognition (NC); (B) mild cognitive impairment (MCI); (C) Alzheimer's disease (AD).

Du et al., JNNP 2001

Instance of the full sequence of hippocampal formation tracings (35-40 slices)

Frisoni et al., Neuroimage, 2006



Raz et al., Neuroimage, 2010

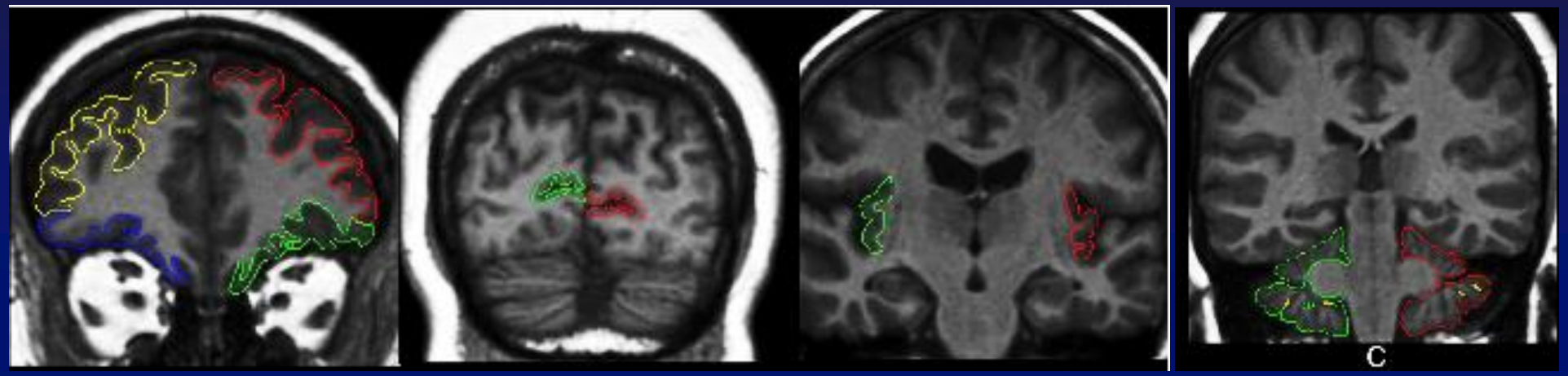
12 ROIs

Lateral and orbitofrontal cortex

Primary visual cortex

Insula

Cerebellum

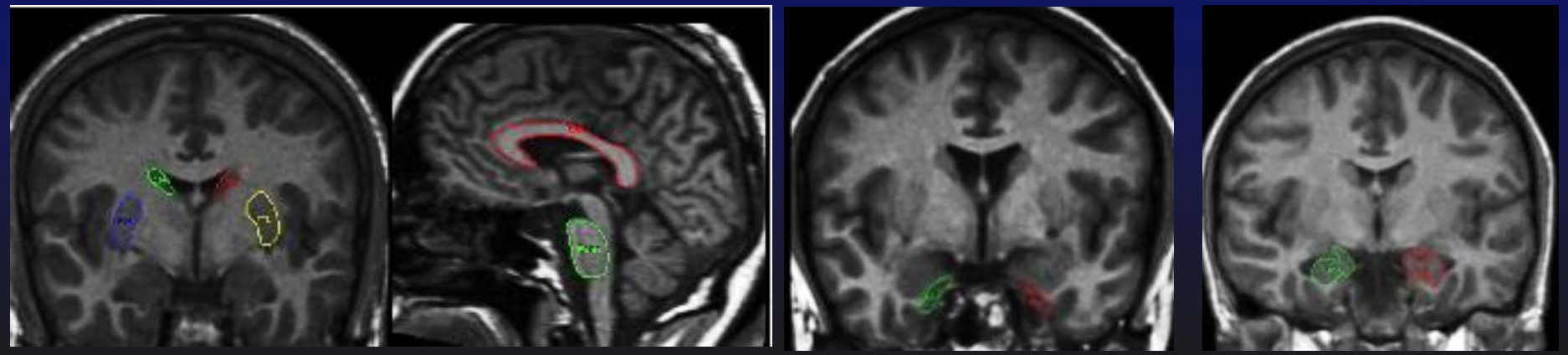


Caudate nucleus
Putamen

Corpus callosus
Pons

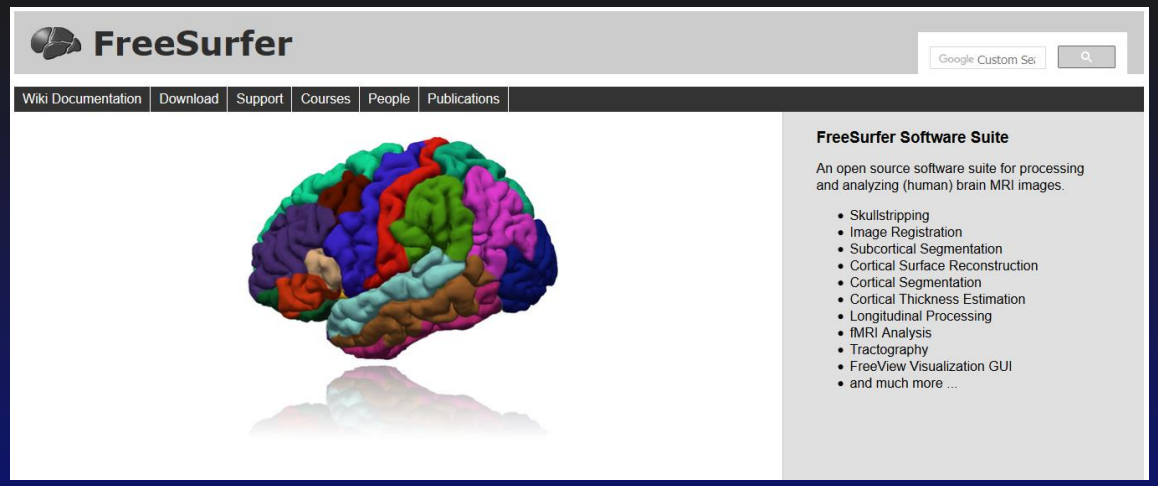
Entorhinal cortex

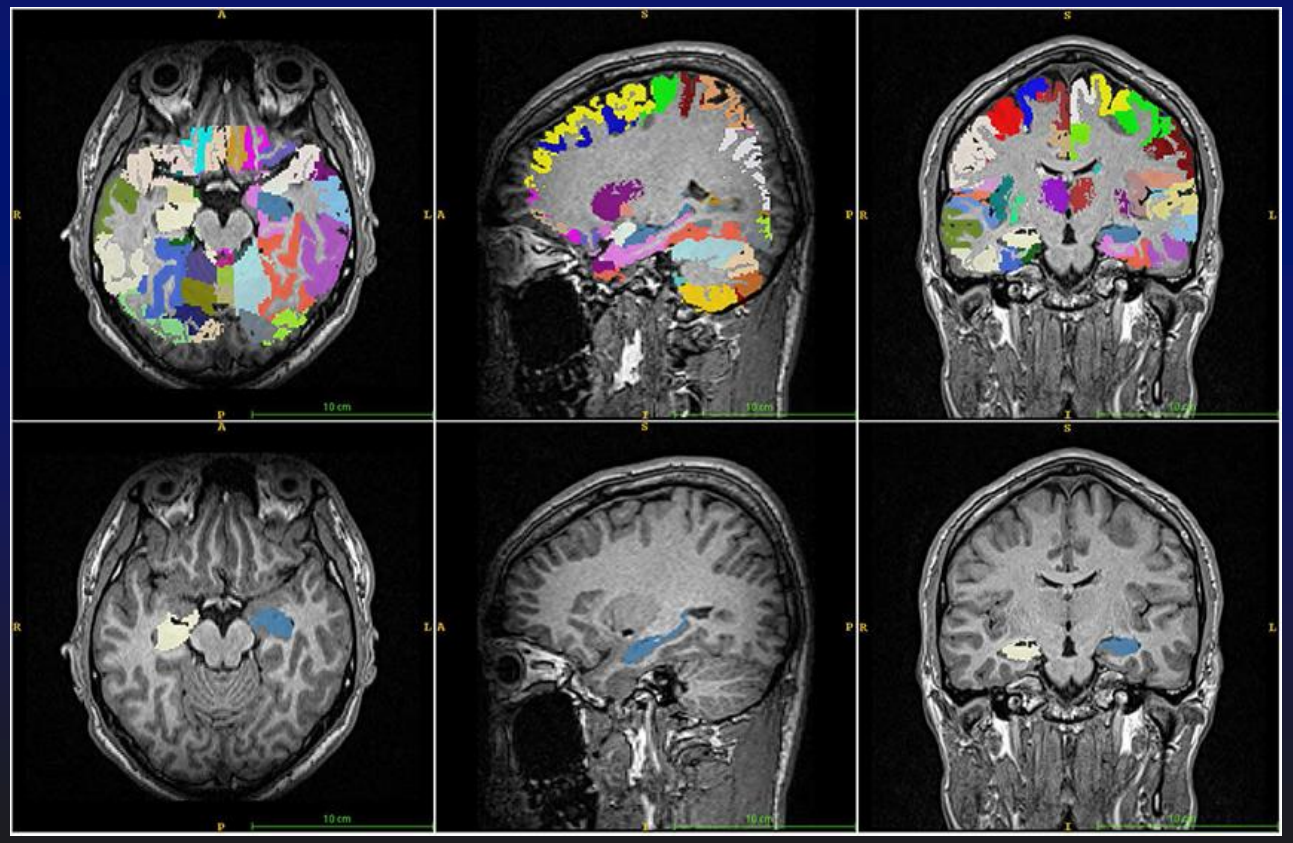
Hippocampus

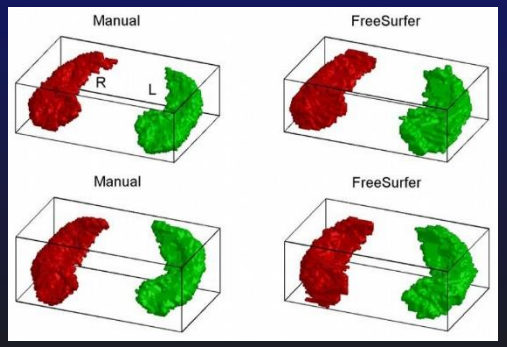


Region-of-interest analyses

Antomatic segmentation





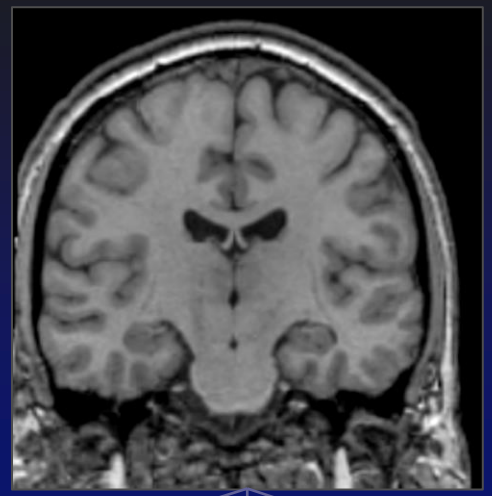


- FSL First: subcortical structures (including the hippocampus)

- HAMMER
- LocalInfo
- ABSS
- IBASPM

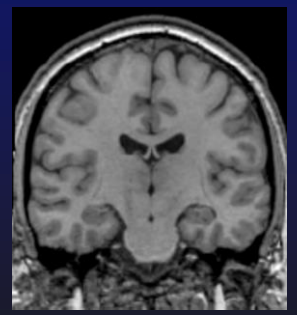
ACQUISITION

Structural MRI (T1-weighted)



PROCESSING AND ANALYSIS

Visual



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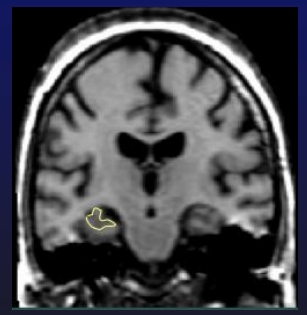
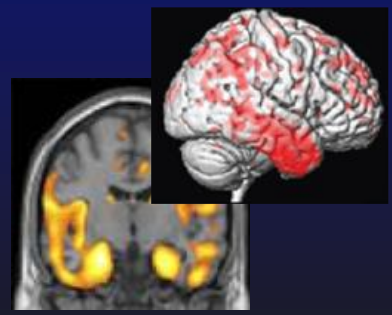
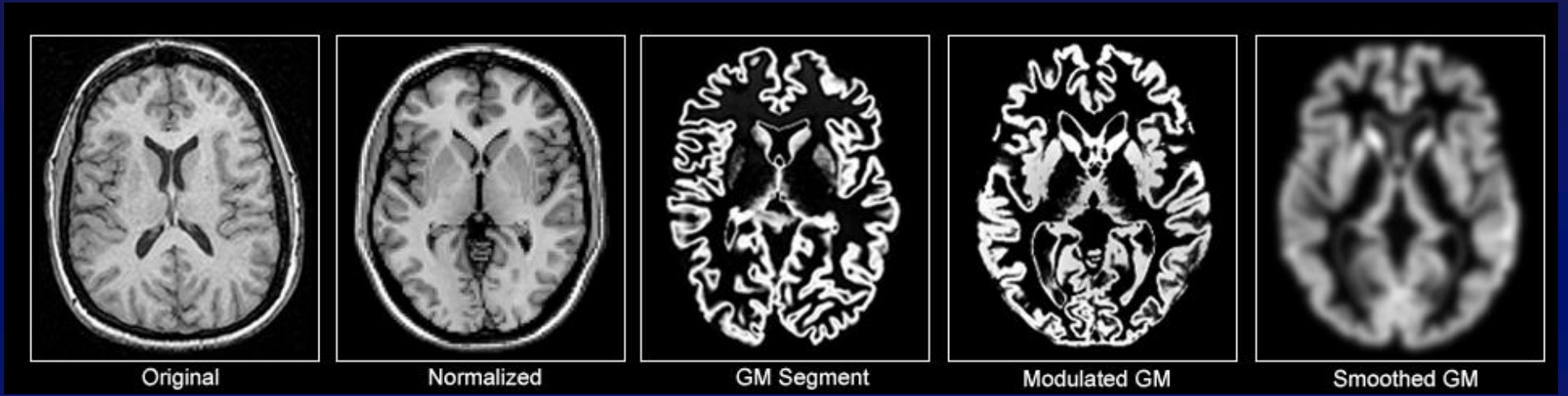


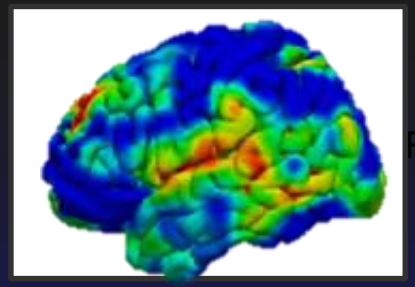
Whole brain techniques

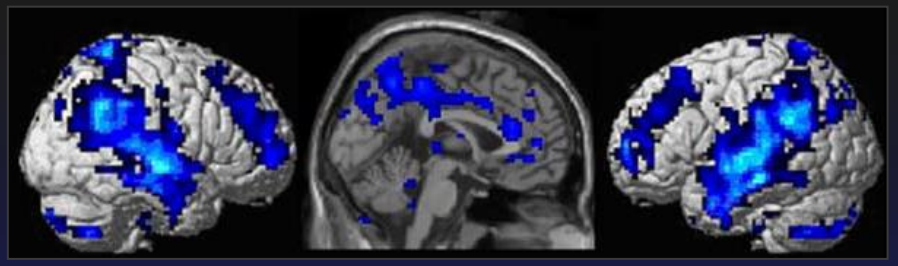


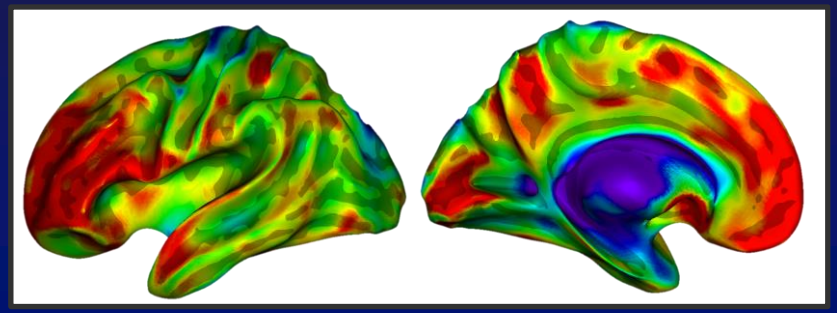
WHOLE-BRAIN/GM ANALYSES

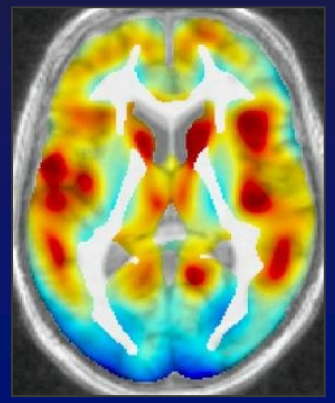
Example: SPM (voxel-based morphometry)

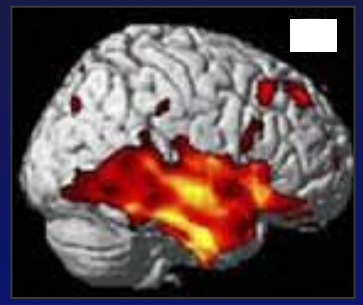


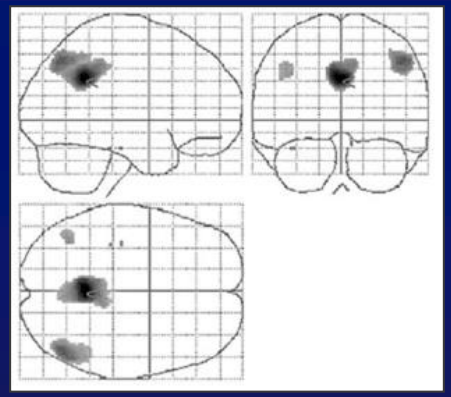


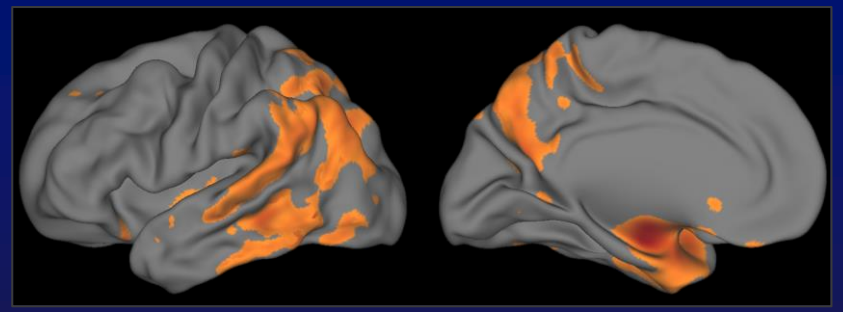


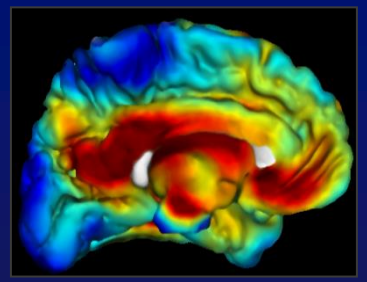


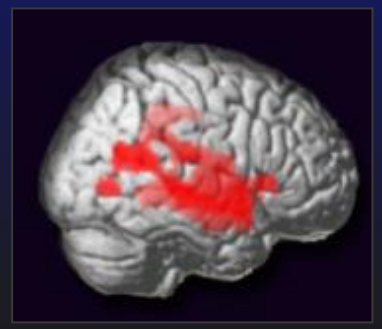


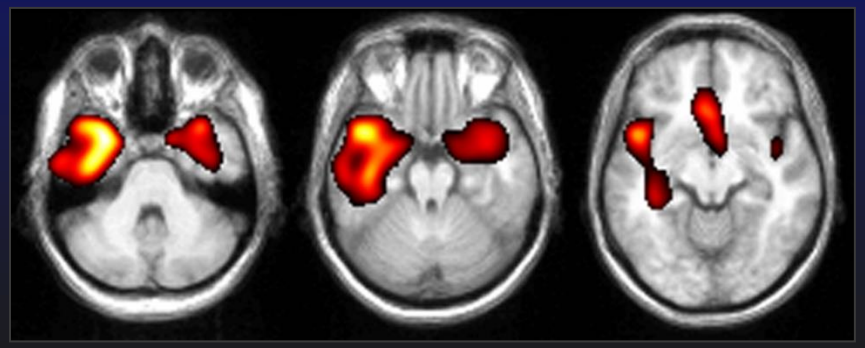






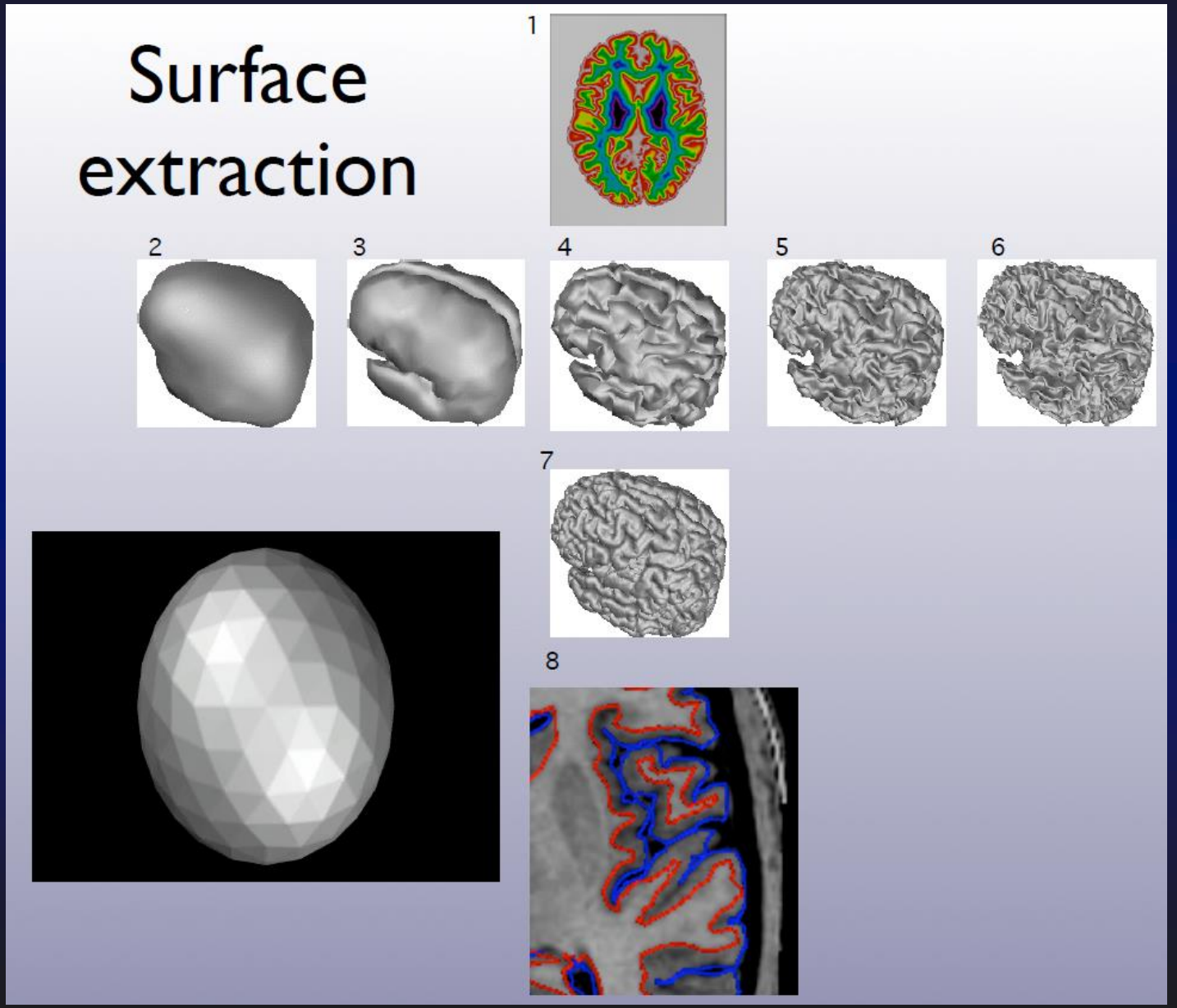






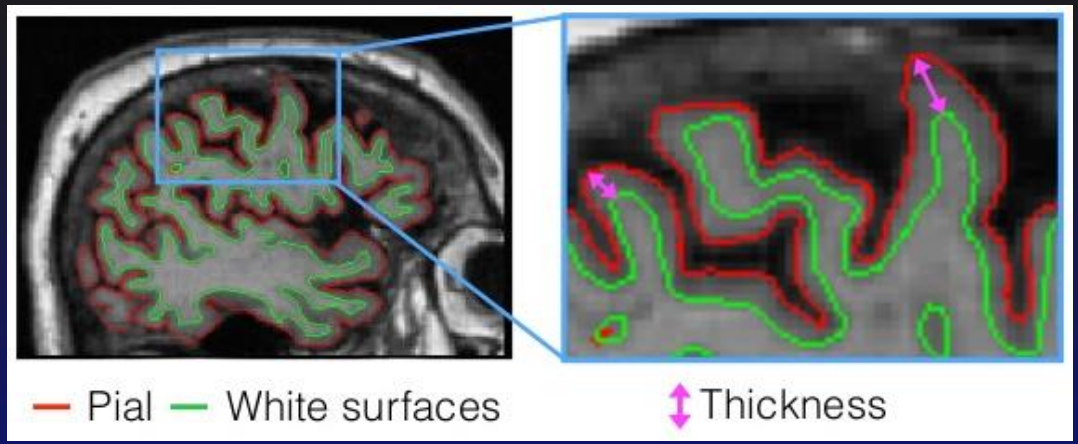
WHOLE-BRAIN/GM ANALYSES

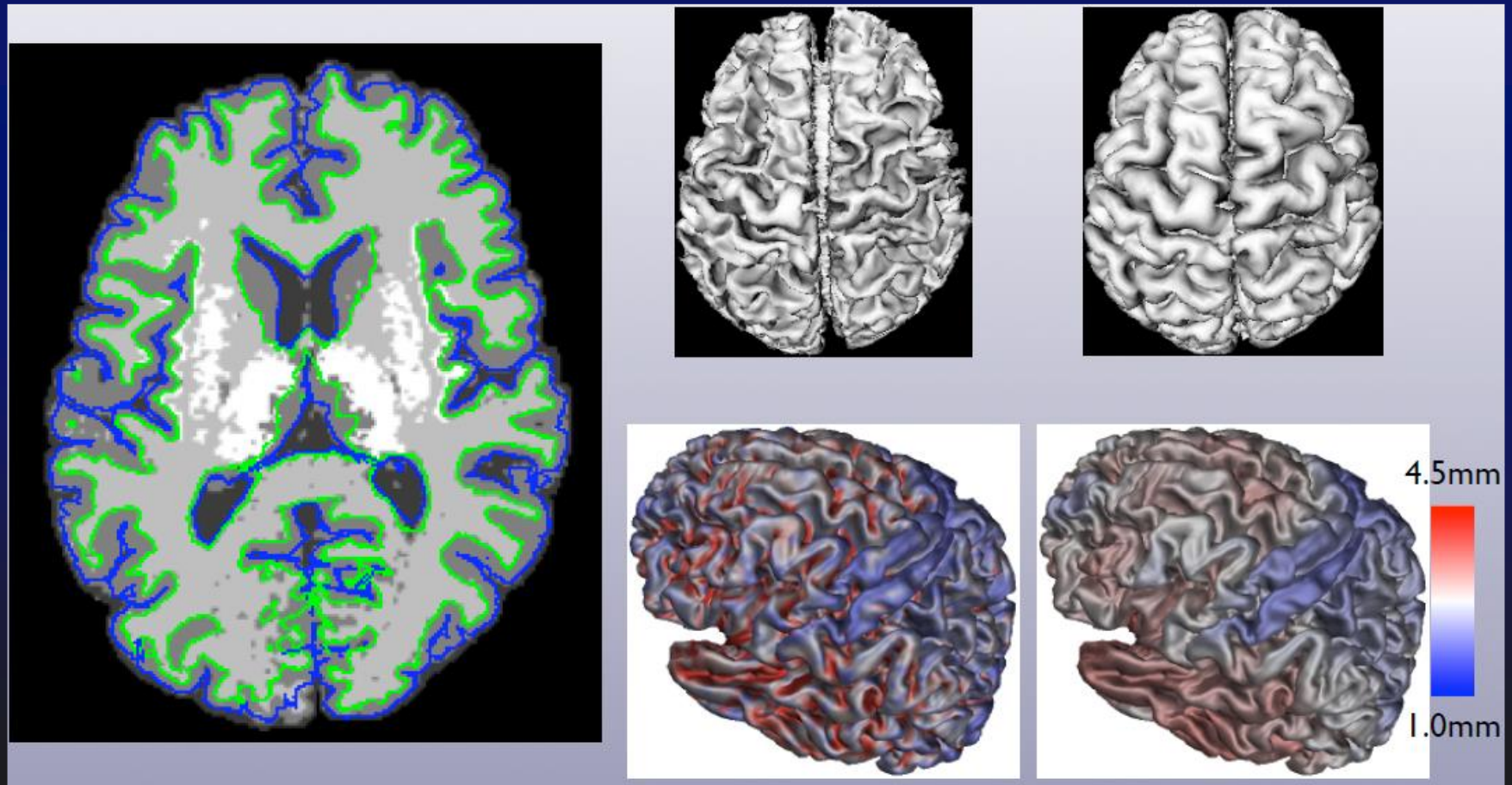
Example: cortical thickness



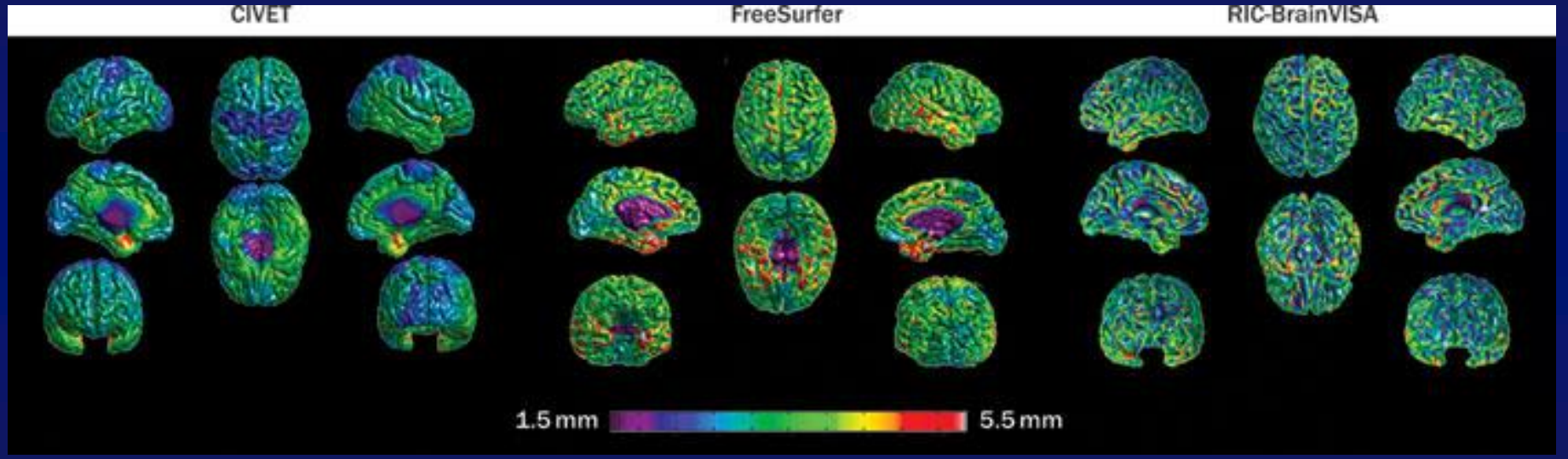
WHOLE-BRAIN/GM ANALYSES

Example: cortical thickness





Maps of mean cortical thickness in the Alzheimer's Disease Neuroimaging Initiative dataset obtained with CIVET, FreeSurfer and RIC-BrainVISA, and displayed with the same visualization tool.



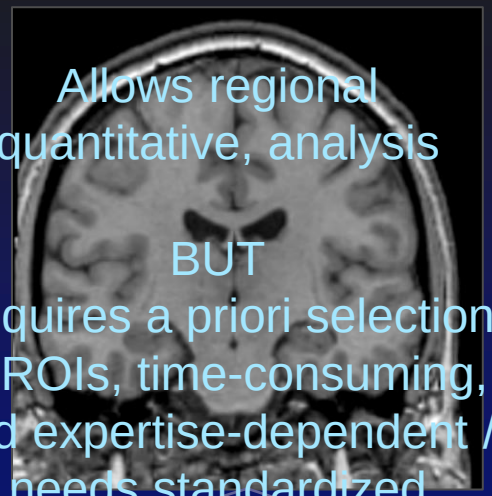
Frisoni et al., 2011

ACQUISITION

Structural MRI (T1-weighted)

Fast, direct, easier for clinician

BUT
Qualitative only, and depends heavily on observer's prior experience and training



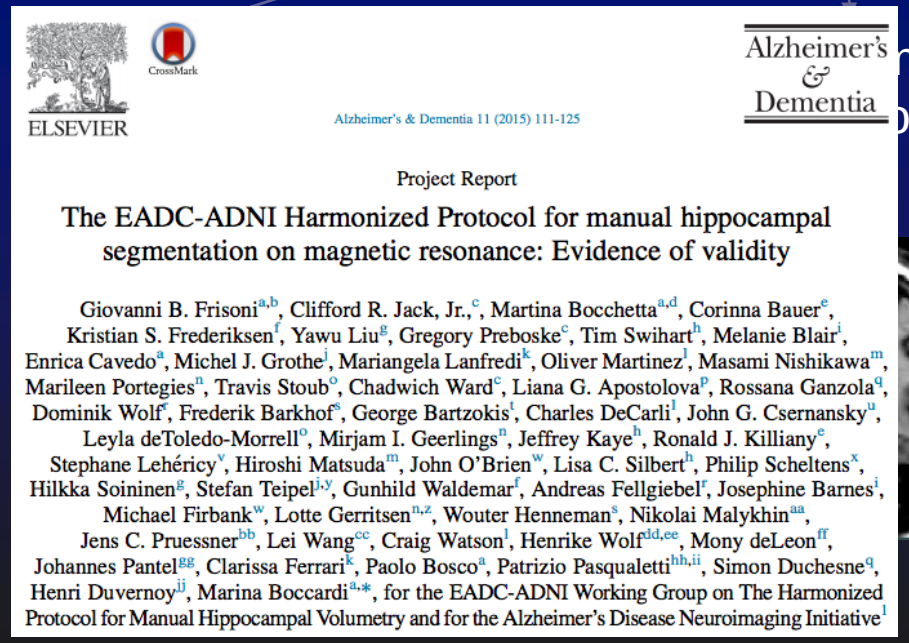
Allows regional quantitative, analysis

BUT
Requires a priori selection of ROIs, time-consuming, and expertise-dependent / needs standardized technique and cut-off

Objective, comprehensive, quantitative, more precise

BUT
Less direct and fast, relies on technology and lack of consensual cut-off -> needs standardisation

PROCESSING AND ANALYSIS



ELSEVIER

CrossMark

Alzheimer's & Dementia 11 (2015) 111-125

Alzheimer's & Dementia

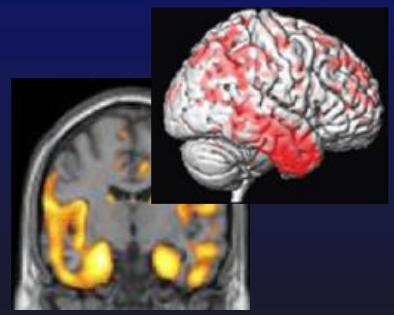
Project Report

The EADC-ADNI Harmonized Protocol for manual hippocampal segmentation on magnetic resonance: Evidence of validity

Giovanni B. Frisoni[a,b], Clifford R. Jack, Jr.,[c], Martina Bocchetta[a,d], Corinna Bauer[e], Kristian S. Frederiksen[f], Yawu Liu[g], Gregory Preboske[c], Tim Swihart[h], Melanie Blair[i], Enrica Cavedo[a], Michel J. Grothe[j], Mariangela Lanfredi[k], Oliver Martinez[l], Masami Nishikawa[m], Marileen Portegies[n], Travis Stoub[o], Chadwich Ward[c], Liana G. Apostolova[p], Rossana Ganzola[q], Dominik Wolf[r], Frederik Barkhof[s], George Bartzokis[t], Charles DeCarli[l], John G. Csernansky[u], Leyla deToledo-Morrell[o], Mirjam I. Geerlings[n], Jeffrey Kaye[h], Ronald J. Killiany[e], Stephane Lehéricy[v], Hiroshi Matsuda[m], John O'Brien[w], Lisa C. Silbert[h], Philip Scheltens[x], Hilkka Soininen[g], Stefan Teipel[j,y], Gunhild Waldemar[f], Andreas Fellgiebel[r], Josephine Barnes[i], Michael Firbank[w], Lotte Gerritsen[n,z], Wouter Henneman[s], Nikolai Malykhin[aa], Jens C. Pruessner[bb], Lei Wang[cc], Craig Watson[l], Henrike Wolf[dd,ee], Mony deLeon[ff], Johannes Pantel[gg], Clarissa Ferrari[k], Paolo Bosco[a], Patrizio Pasqualetti[hh,ii], Simon Duchesne[q], Henri Duvernoy[jj], Marina Boccardi[a,*], for the EADC-ADNI Working Group on The Harmonized Protocol for Manual Hippocampal Volumetry and for the Alzheimer's Disease Neuroimaging Initiative[t]

anual or
ons of interest

Whole brain techniques



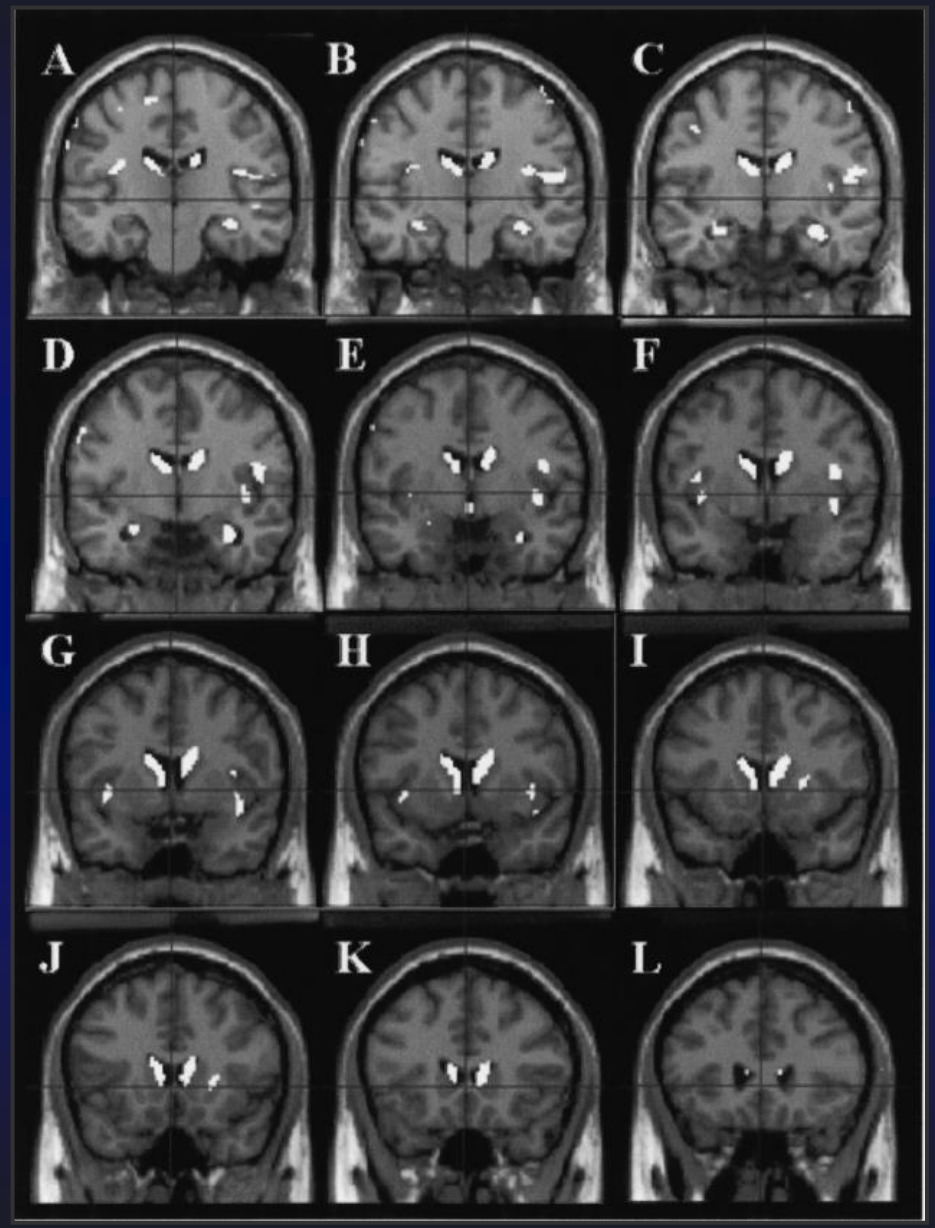
www.hippocampal-protocol.net

Include here interactive questions:

Part I: score hippocampal atrophy (visual rating scale)

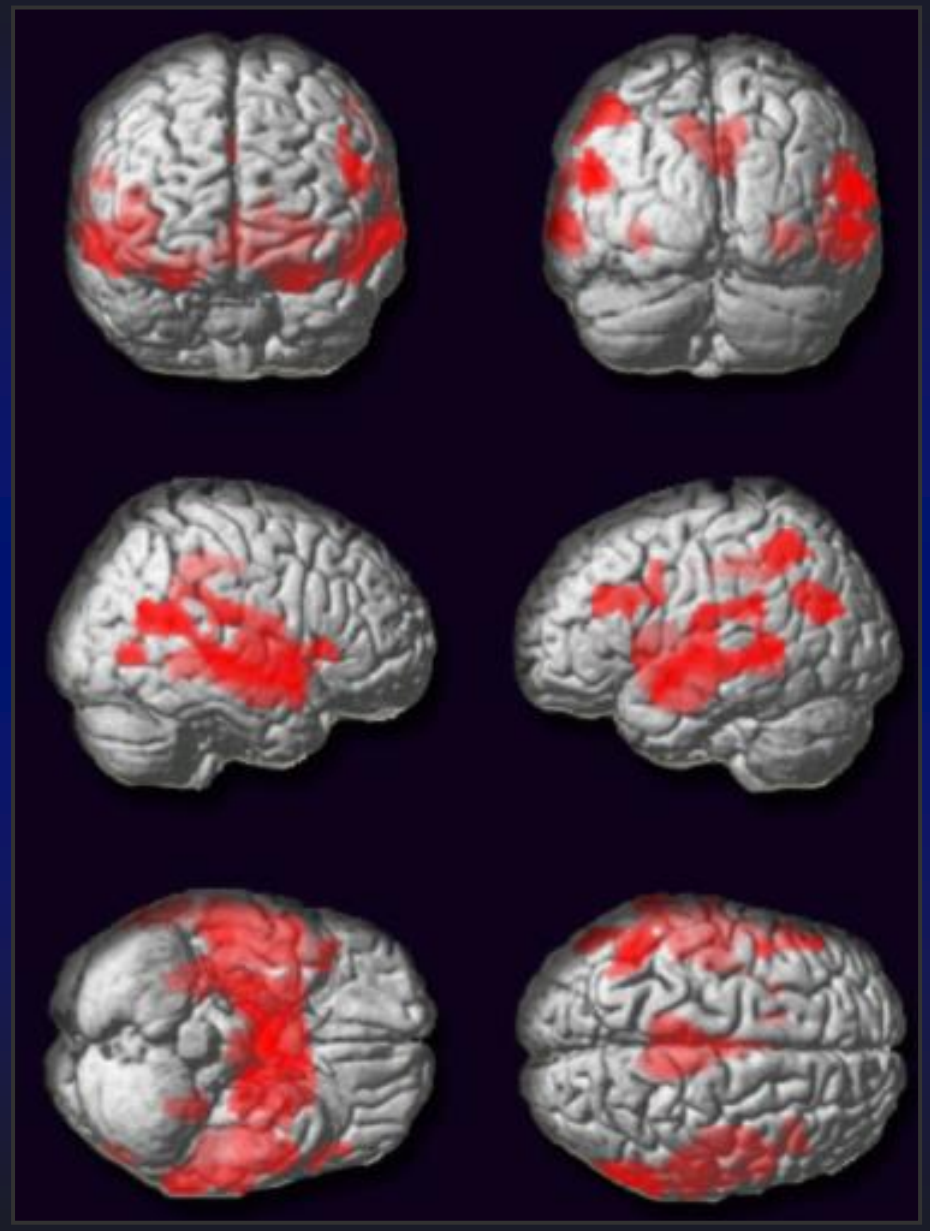
- **Topography of cortical atrophy in AD**

Voxel-based morphometry (VBM – SPM)



7 AD / 7 controls

Rombouts et al., 2000

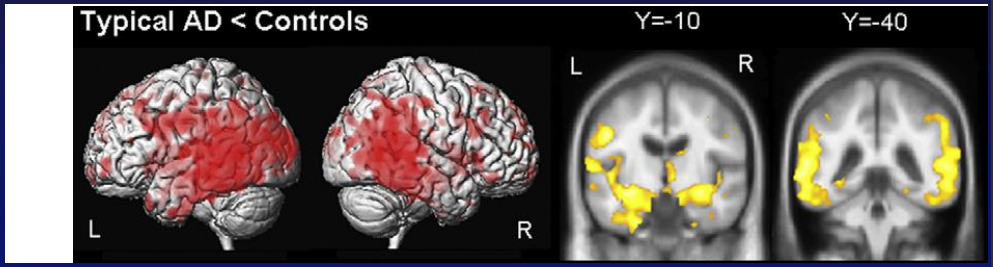


19 AD / 16 controls

Baron et al., 2001

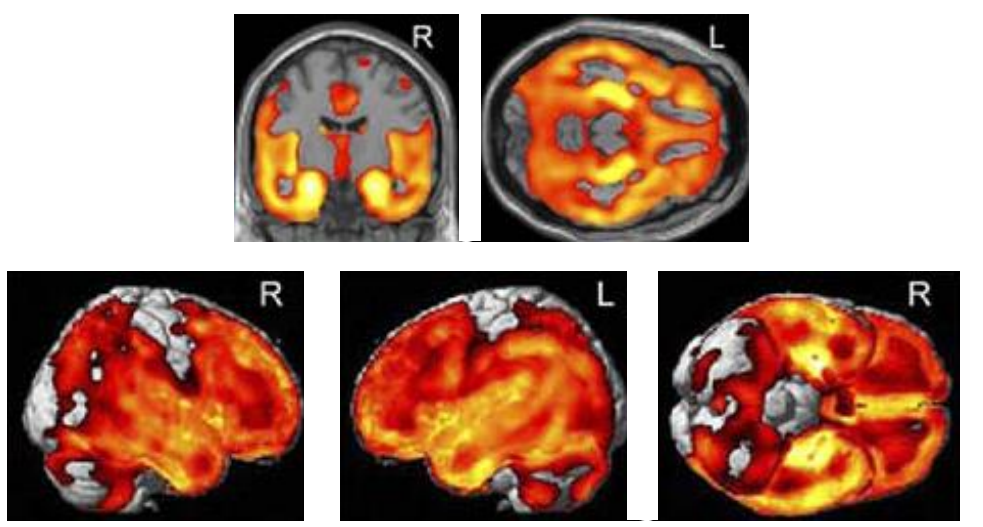
Voxel-based morphometry (VBM – SPM)

Patients with a neuropathological confirmation

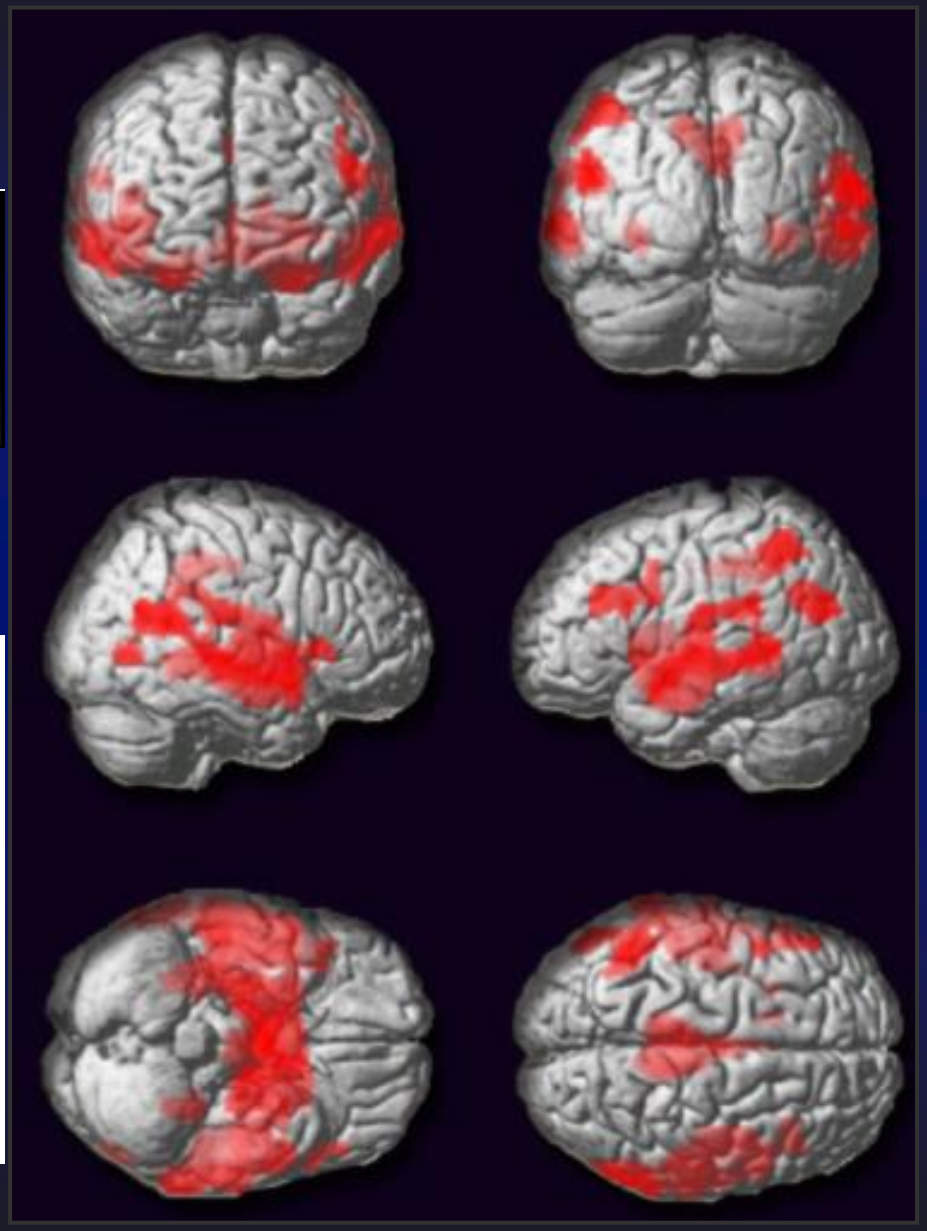


14 AD / 20 controls *Whitwell et al., 2011*

With large cohorts…



206 SAS / 148 MA *Risacher et al., 2008*



19 AD / 16 controls Baron et al., 2001

Ossenkoppele et al., 2015

- 93 posterior cortical atrophy (PCA)

- 74 logopenic variant primary progressive aphasia (lvPPA)

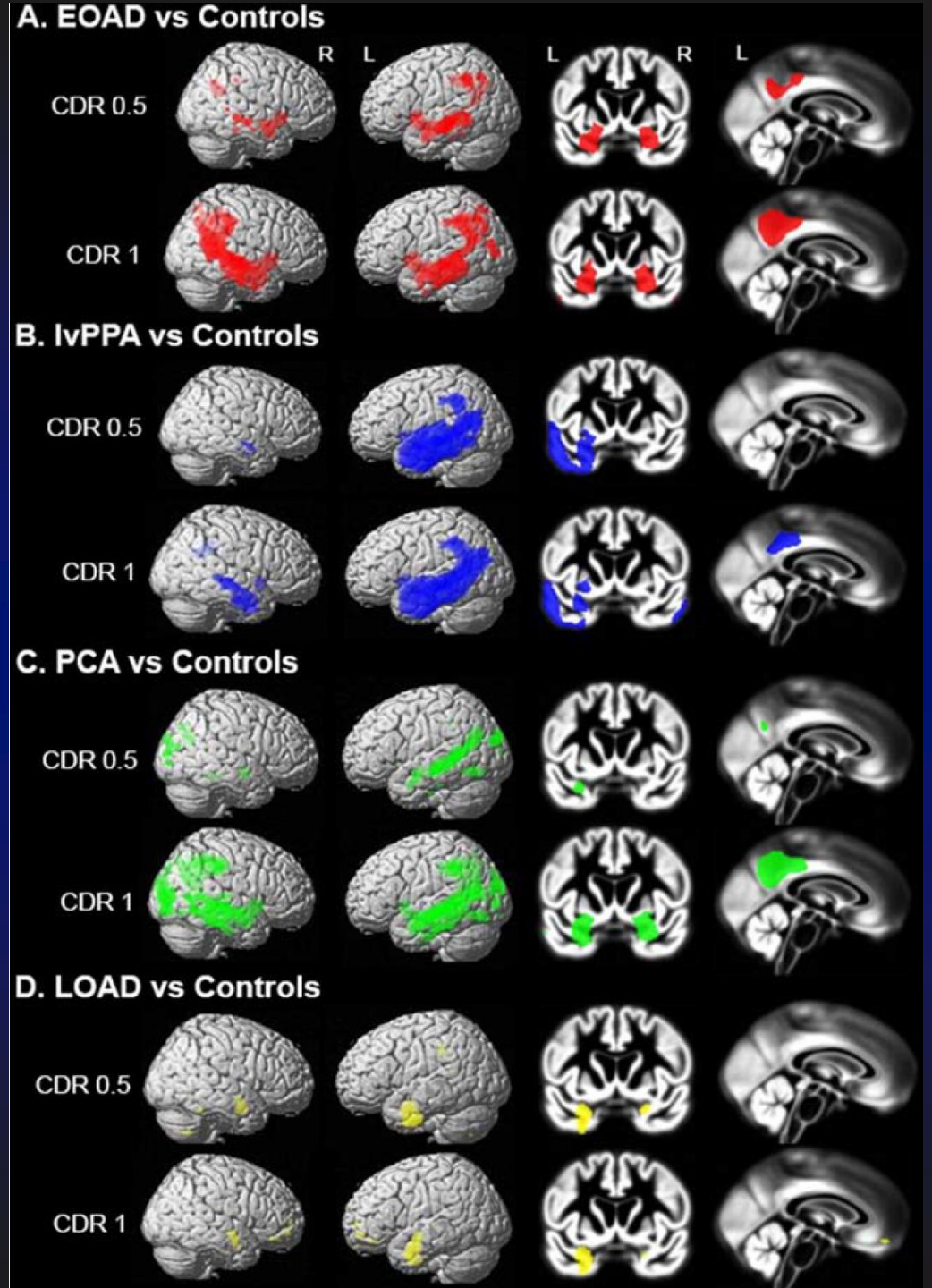
- 114 early and 114 late age-of-onset memory-predominant AD

PCA patients → most prominent visuospatial deficits

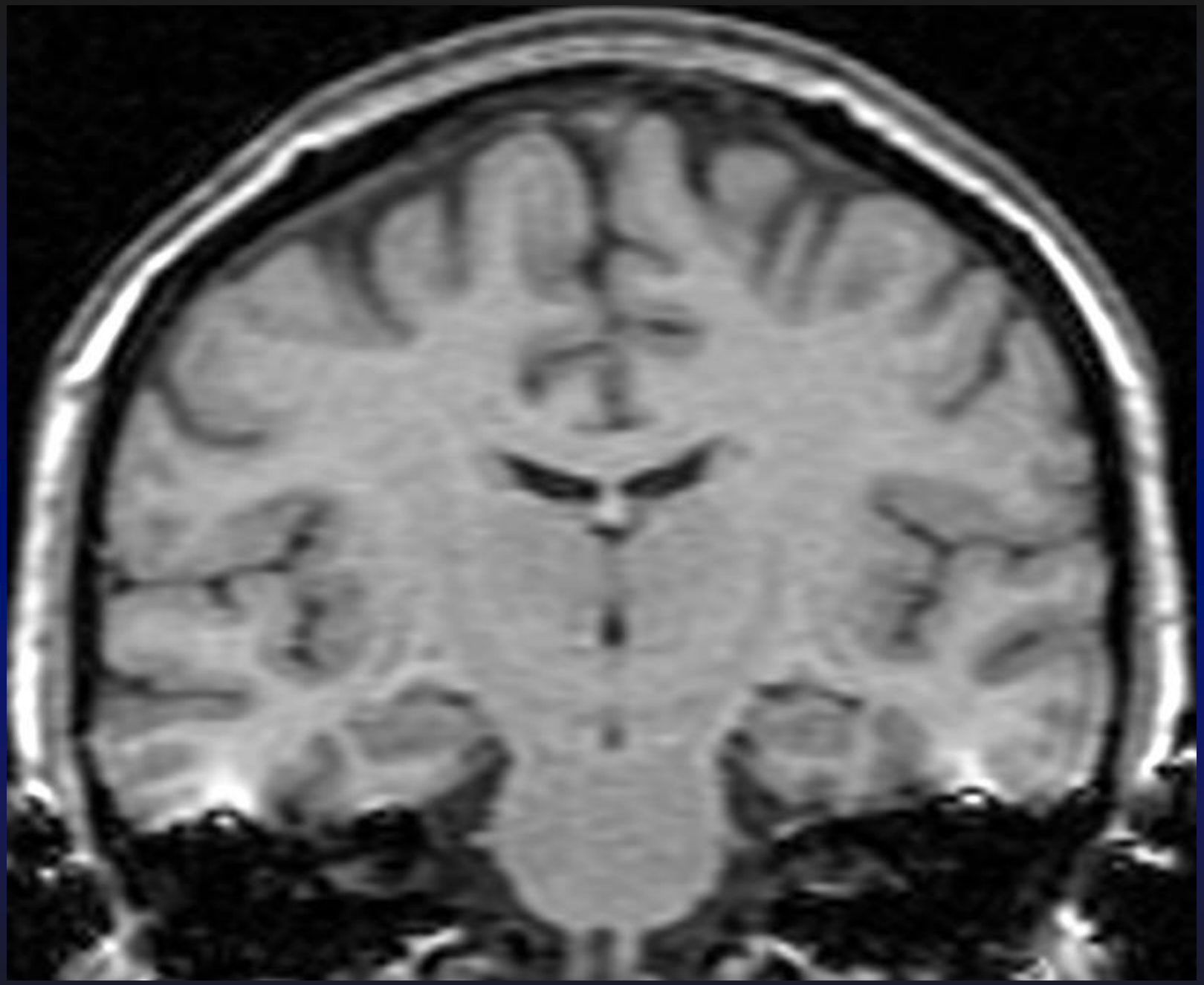
lvPPA patients → most impaired in the language domain

LOAD and EOAD patients → memory-predominant neuropsychological profile

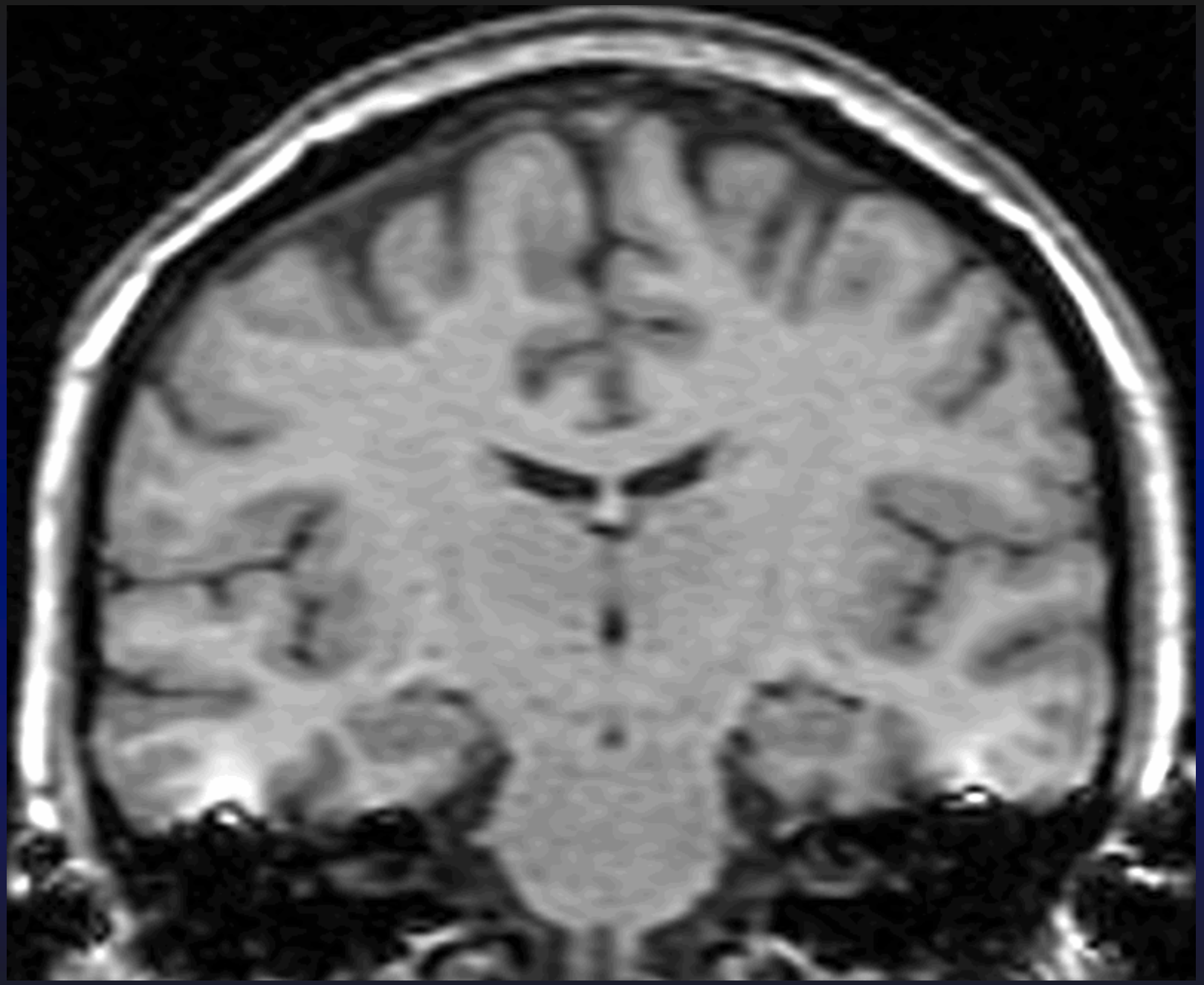
Early syndrome-specific atrophy mirrored functional brain networks underlying functions that are uniquely affected in each variant: **Language network in lvPPA**, **posterior cingulate cortex-hippocampal circuit in amnestic EOAD** and **LOAD**, and **visual networks in PCA**. At more advanced stages, atrophy patterns largely converged across AD variants.



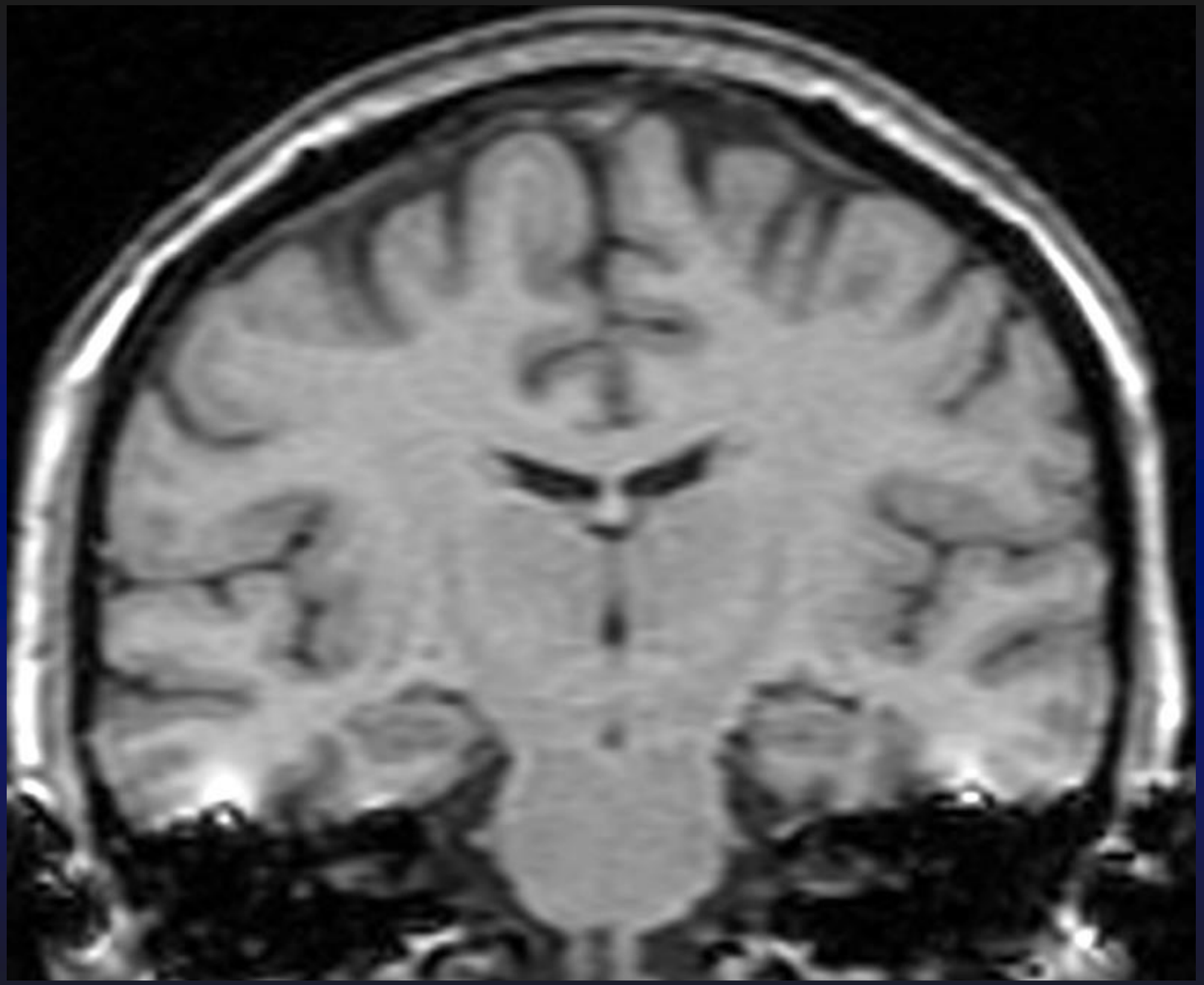
- **Longitudinal structural MRI to track disease progression**



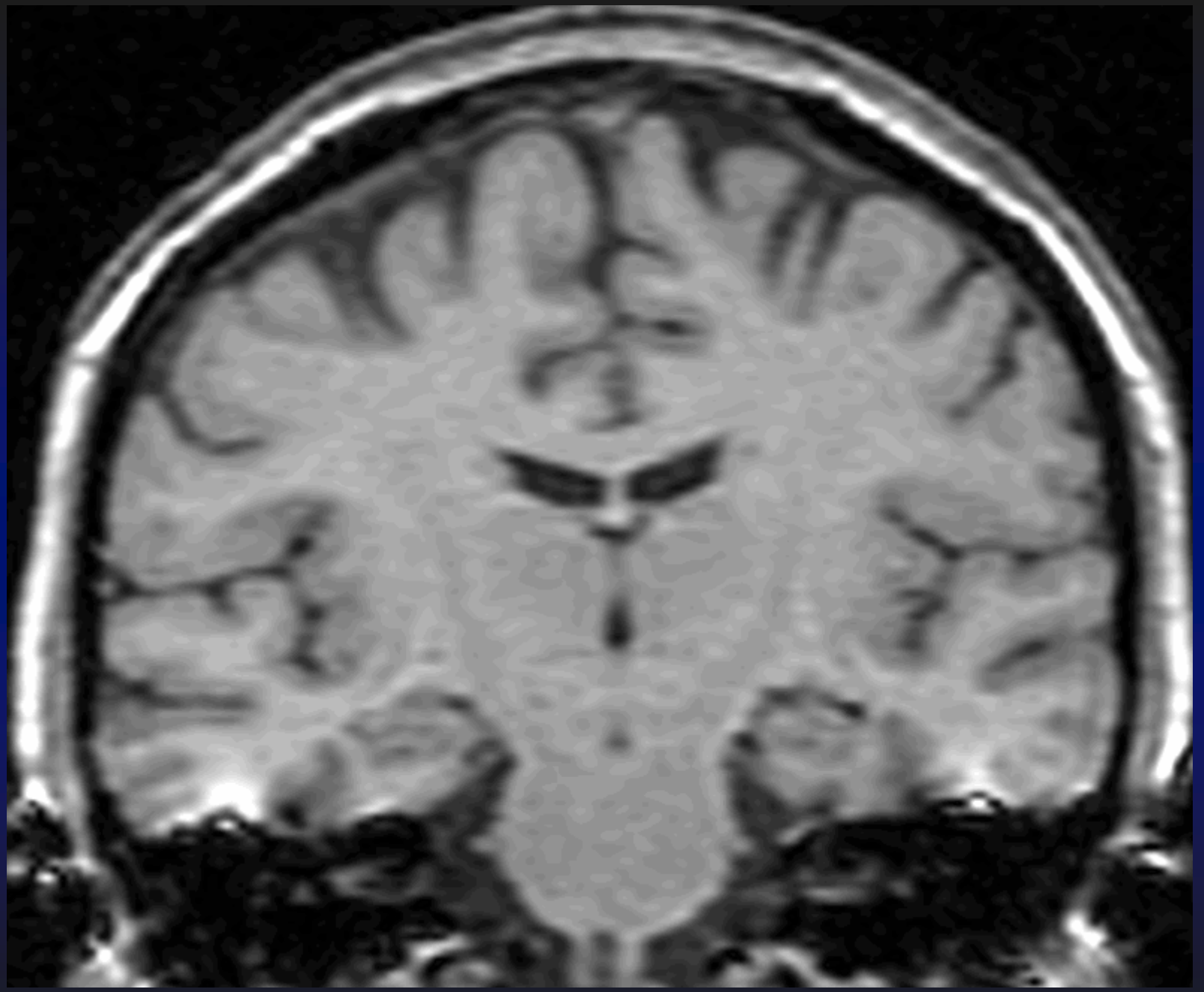
Courtesy of Nick Fox



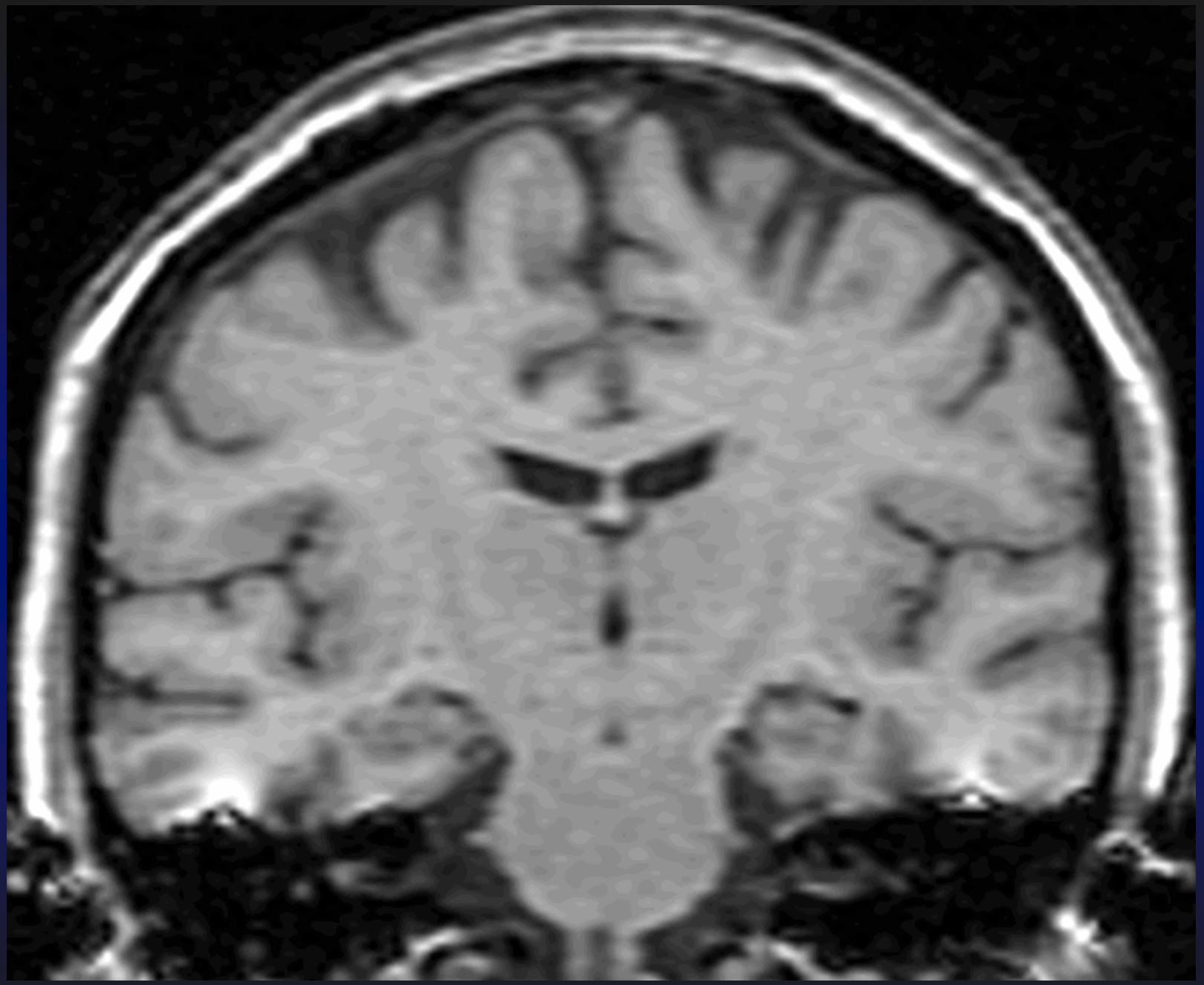
Courtesy of Nick Fox



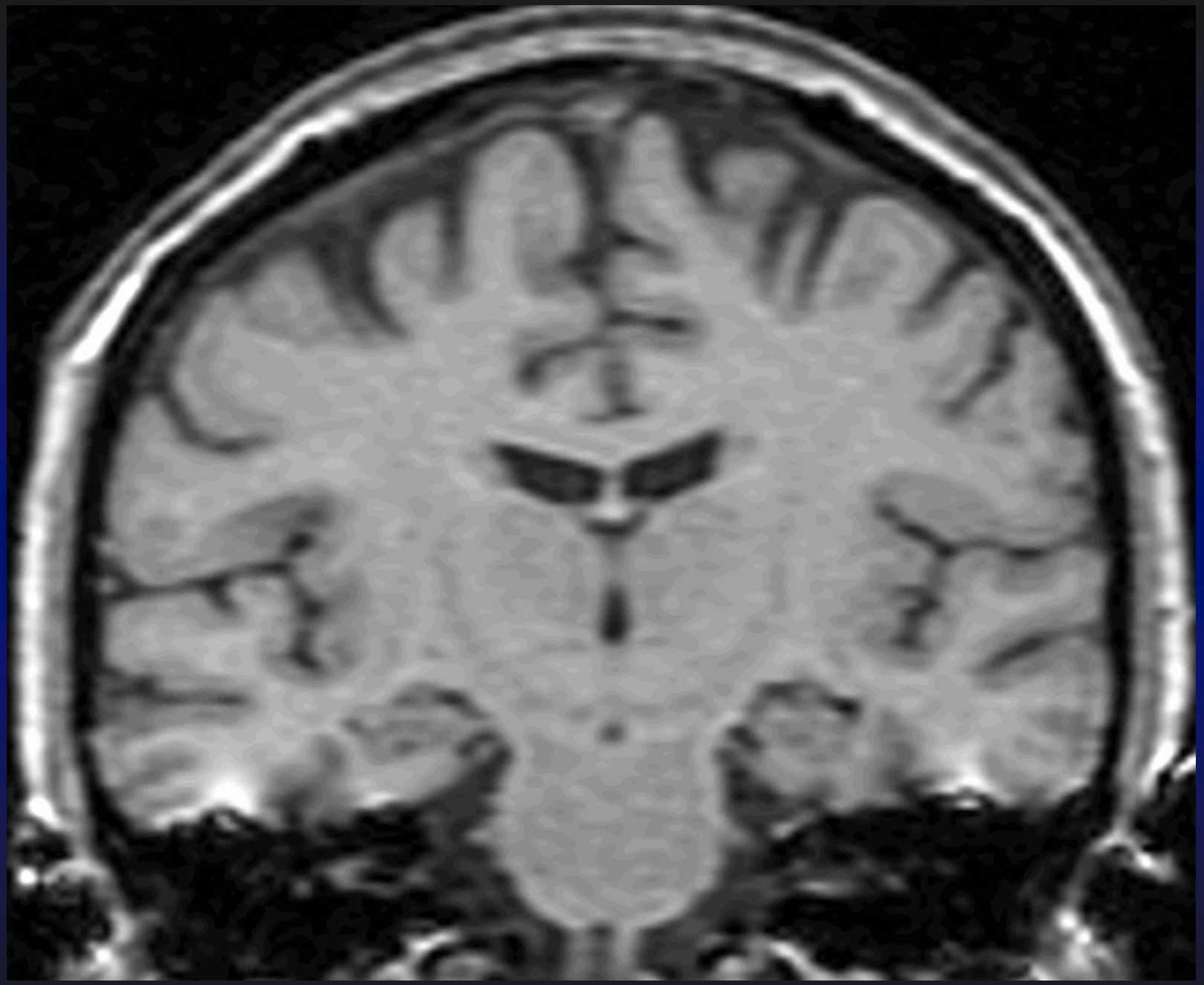
Courtesy of Nick Fox



Courtesy of Nick Fox

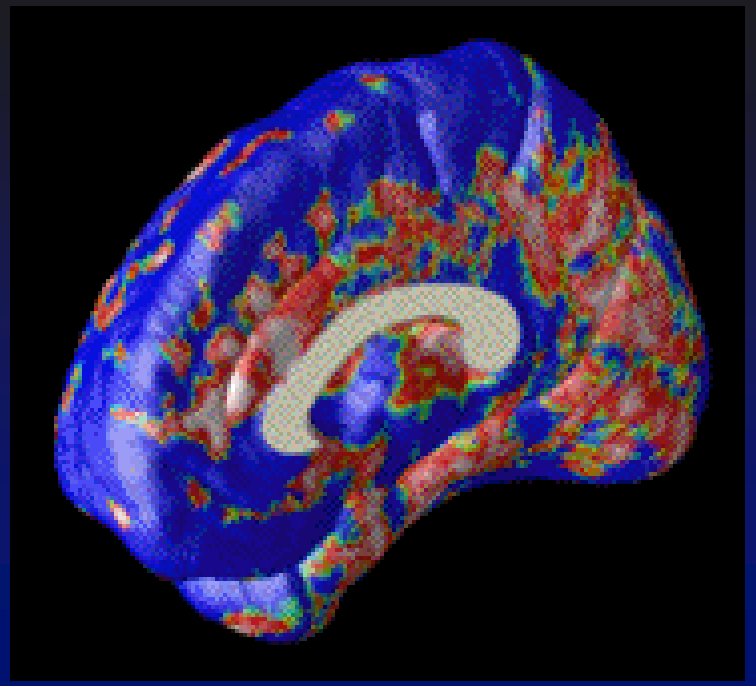


Courtesy of Nick Fox

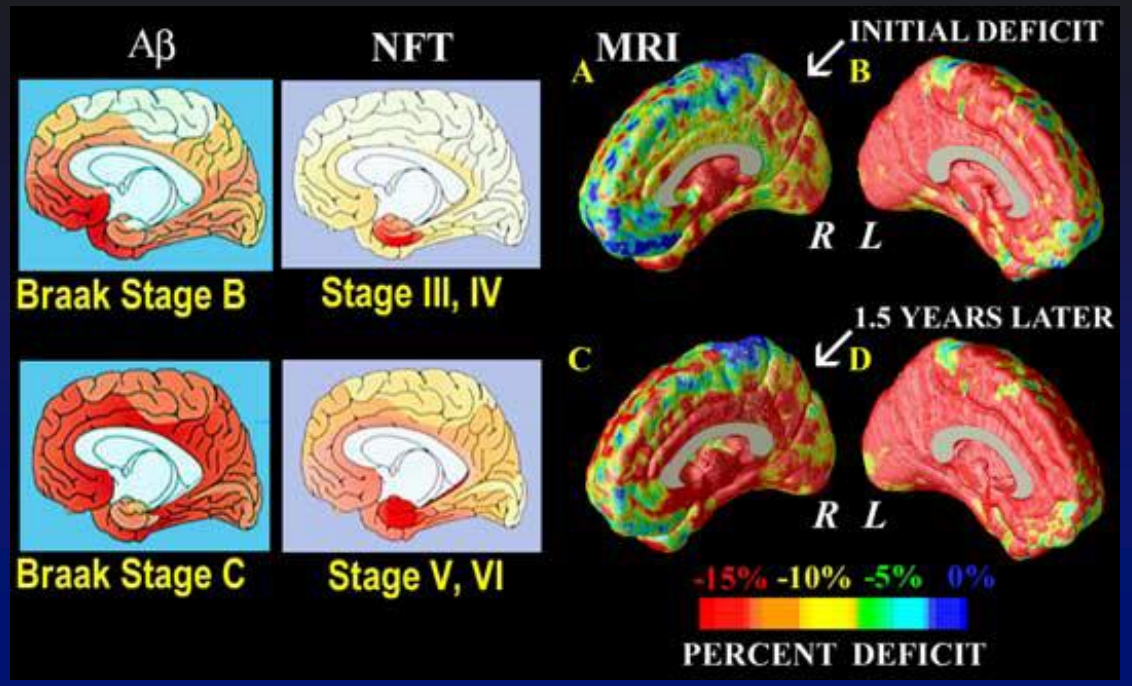


Courtesy of Nick Fox

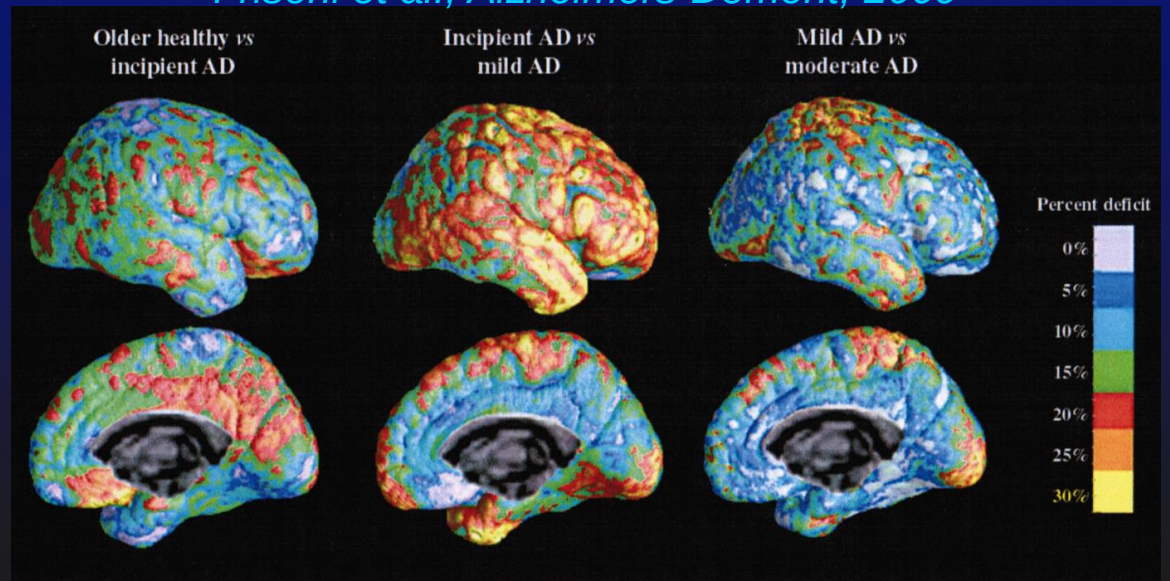
Thompson et al., J Neurosci, 2003

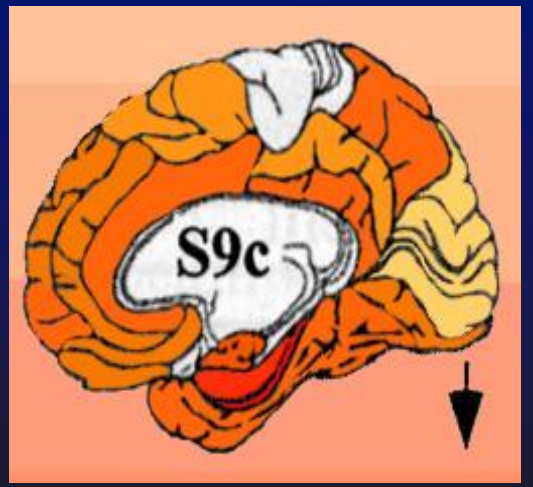


Thompson et al., Ann N Y Acad Sci, 2007

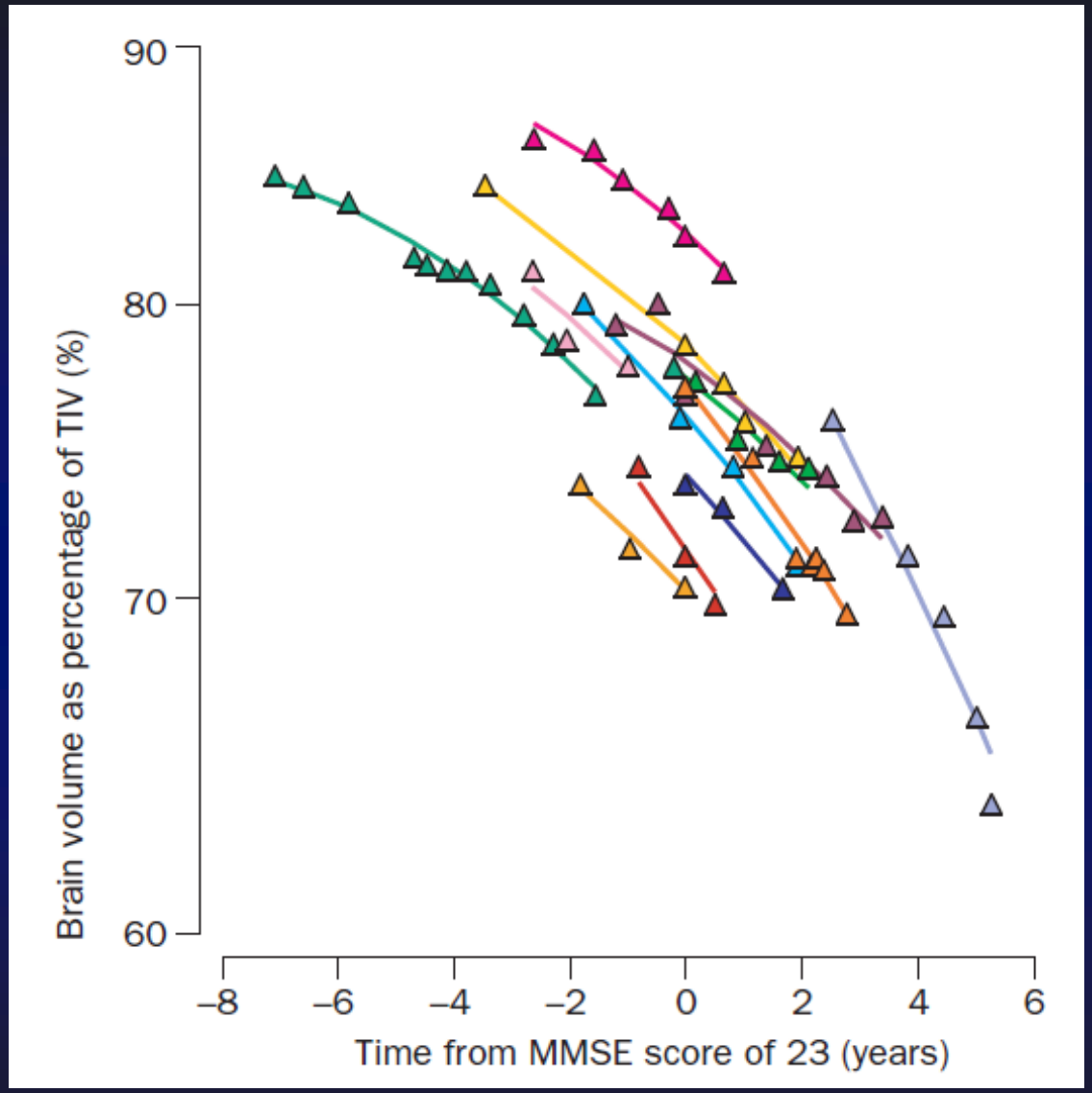


Cavedo & Frisoni, QJNuclMedMolImaging, 2011 from Frisoni et al., Alzheimers Dement, 2009





Braak & Braak, Duyckaerts et al., Delacourte et al.,



The rate of atrophy increases as the disease progresses

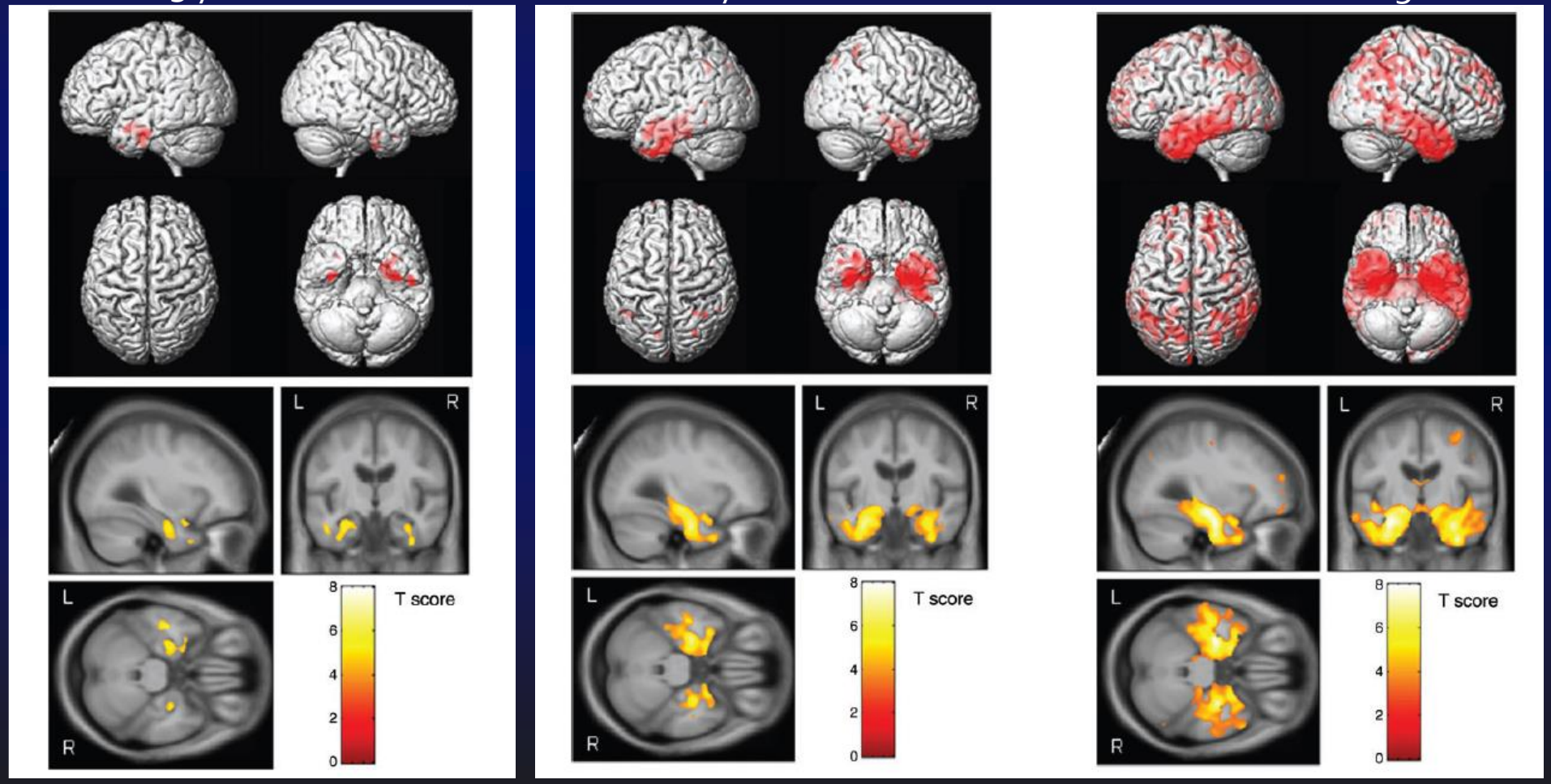
Chan et al., Lancet, 2003

Longitudinal studies:
Transition from MCI to AD

3 yrs before

1 yr before

AD dementia diagnosis

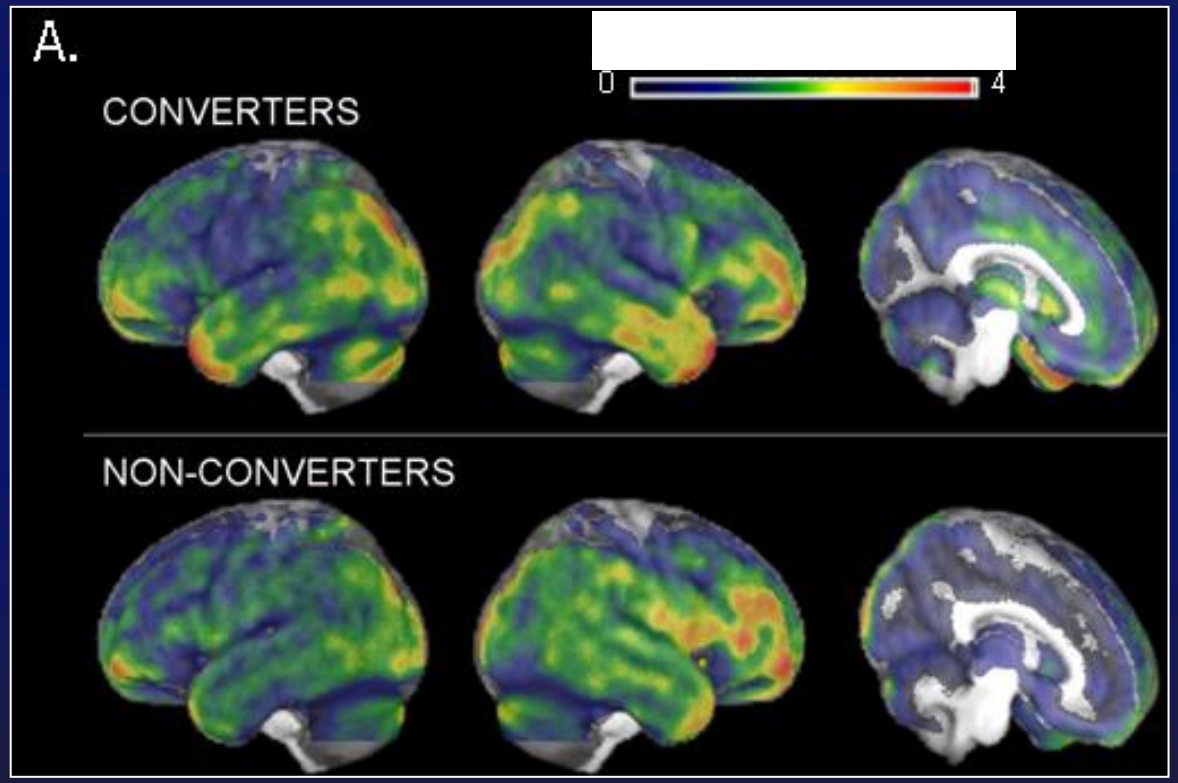


33 SAS / 33 MCI converters

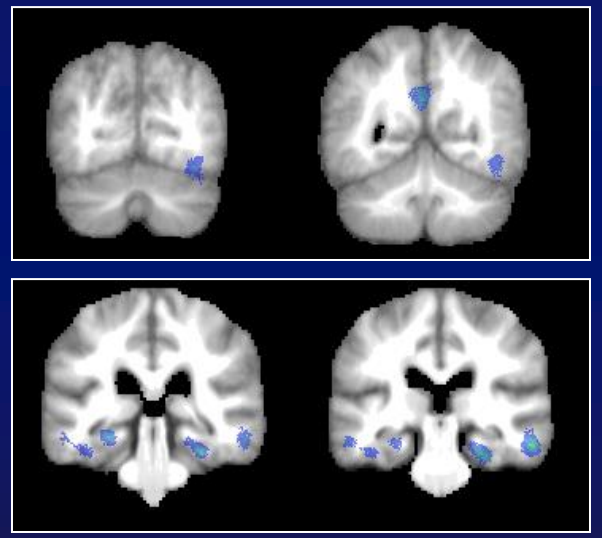
Whitwell et al., Brain 2007

Longitudinal studies:
Transition from MCI to AD

Evolution of atrophy over 18 months



Significantly higher GM loss from baseline to follow-up in converters compared to non-converters

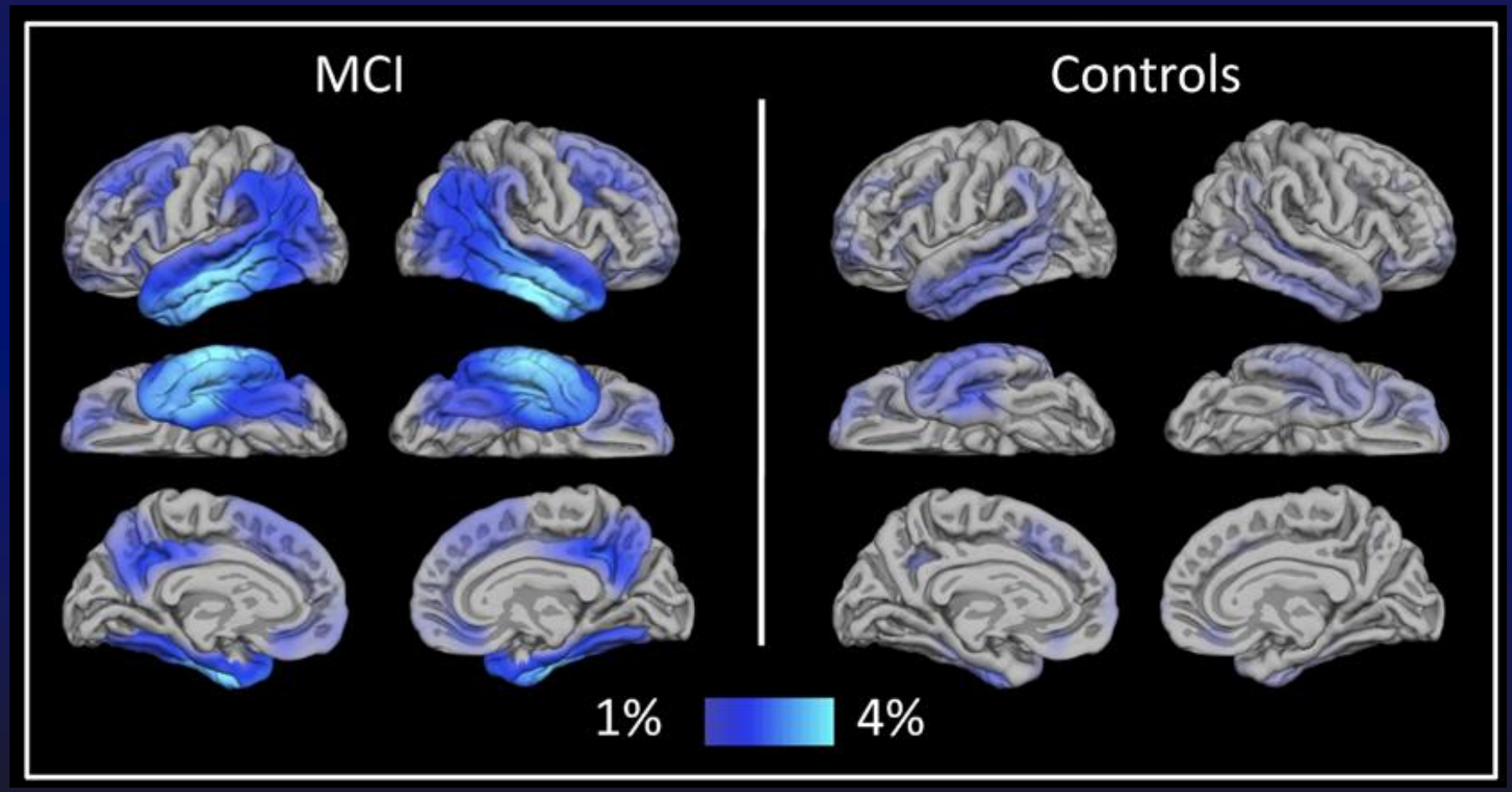


Inf and middle temporal cortex
Hippocampup
Fusiform gyrus
Posterior cingulate cortex

11 MCI non converters / 7 MCI converters

Chételat et al., 2005

Longitudinal studies:
Differences from normal aging

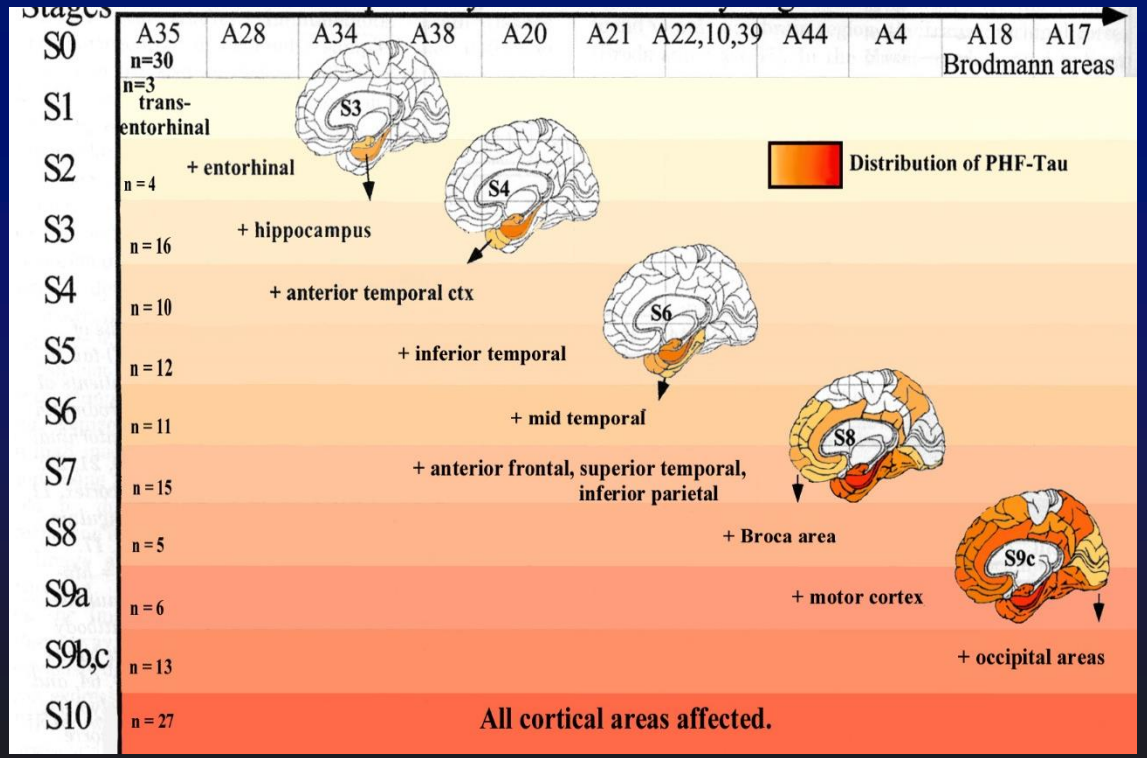


103 MCI / 90 SAS

McDonald et al., 2010

Evolution of atrophy - Summary

- START: medial temporal lobe (entorhinal, hcp ++) even before the MCI stage
- Progress to temporal neocortex, then parietal (and frontal) in AD dementia
- Accelerates with the progression of the disease → importance of early diagnosis
- The profile is close to that of NFT



Delacourte et al., 1999

Include here interactive questions:

Part II: order MRI scans (longitudinal study)

The hippocampus in Alzheimer's disease (AD)

1) Introduction: epidemiology, neuropathology and clinical diagnosis
2) Neuroimaging techniques and new criteria
3) Profile of atrophy in AD: from regions-of-interest to voxelwise analyses
4) **A differential effect of AD on hippocampal subfields**
5) Hippocampal circuitry and connectivity
6) Beyond the hippocampus: hippocampal networks

Hippocampal atrophy: LACK OF SPECIFICITY

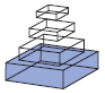
Disorder	*Number of studies*	*General findings*
Temporal lobe epilepsy	84	↓ Hippocampi, most pronounced ipsilateral to epileptic focus
Schizophrenia	76	↓/↔ Hippocampi bilaterally
Alzheimer's disease	56	↓ Hippocampi bilaterally; marker for temporal lobe degeneration
Normal controls	44	Hippocampal volume is dependent on gender, handedness, and age
Other epilepsy	23	↓ Hippocampi bilaterally
Major depression	20	↔/Recently ↓ hippocampi bilaterally have been demonstrated
Aged	15	Smaller hippocampi are associated with normal aging
PTSD	14	↓/↔ Smaller hippocampi bilaterally
Other dementia	11	↓ Hippocampi
Alcoholism	9	↓/↔ Hippocampi bilaterally
Bipolar disorder	7	↓/↑ Hippocampal volume
Mild cognitive impairment	7	Hippocampal volume loss predictive of conversion to AD
TBI	6	↓ Hippocampi bilaterally
Autism	5	↓/↑ Hippocampal volume
Down's syndrome	5	↓ Hippocampal volume bilaterally
APOE-epsilon 4 allele pos	3	Additionally ↓ hippocampi compared to controls
Borderline personality disorder	3	↓ Hippocampi bilaterally
Febrile seizures	3	↓/↔ Hippocampi
Herpes simplex	3	↓ Hippocampi
Korsakoff's syndrome	3	↓/↔ Hippocampi
OCD	3	↓/↔ Hippocampi bilaterally
Amnesia	2	↓ Hippocampi bilaterally which correlates with impaired memory
Cardiac arrest	2	↓ Hippocampi
Cushing's disease	2	↓ Hippocampi bilaterally; volume increases after treatment
Fragile X syndrome	2	↑ Hippocampi bilaterally
Low birth weight	2	↓ Hippocampi
Panic disorder	2	↔ Hippocampi compared to controls
Parkinson's disease	2	↓ Hippocampi bilaterally
ADHD	1	↔ Hippocampi compared to controls
Anorexia nervosa	1	↔ Hippocampi compared to controls
Antisocial personality disorder	1	Volume of posterior hippocampi negatively correlated to psychopathy
Breast cancer surgery	1	↓ Left hippocampi in women with distressing recollections
Congenital adrenal hyperplasia	1	↔ Hippocampi compared to controls
Fetal alcohol syndrome	1	↔ Hippocampi compared to controls
Huntington	1	↓ Hippocampi bilaterally
Sleep apnea	1	↓ Gray matter concentration in hippocampi
Turner's syndrome	1	↓ Hippocampi bilaterally

↓ = smaller ↑ = larger ↓/↑ = both smaller and larger hippocampal volumes haven been reported ↔ no significant changes ↓/↔ = both smaller and no significant studies have been reported.

Geuze et al. Molecular Psychiatry 2005;10:160-184

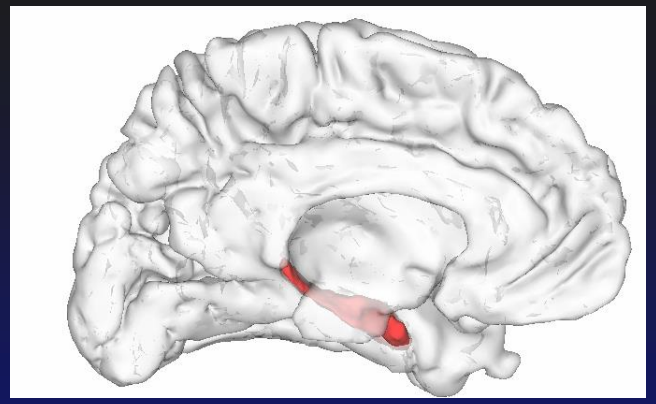
frontiers in
CELLULAR NEUROSCIENCE

REVIEW ARTICLE
published: 31 March 2014
doi: 10.3389/fncel.2014.00095

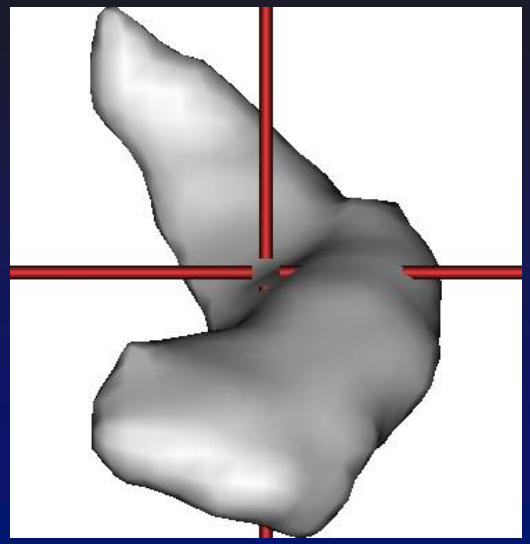


Why looking at the whole hippocampus is not enough—a critical role for anteroposterior axis, subfield and activation analyses to enhance predictive value of hippocampal changes for Alzheimer's disease diagnosis

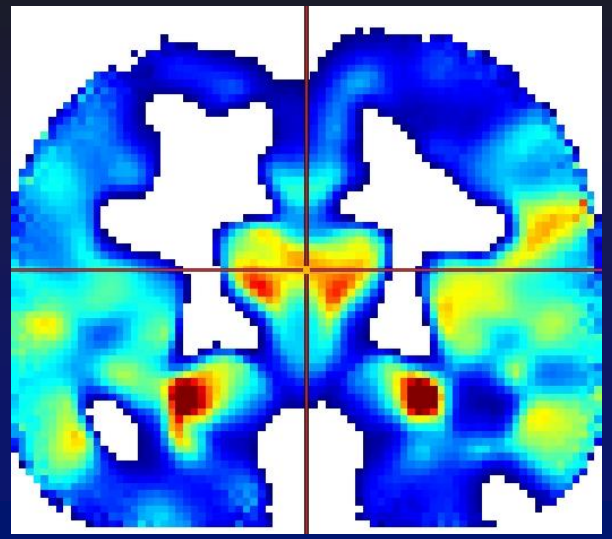
*Aleksandra Maruszak and Sandrine Thuret**



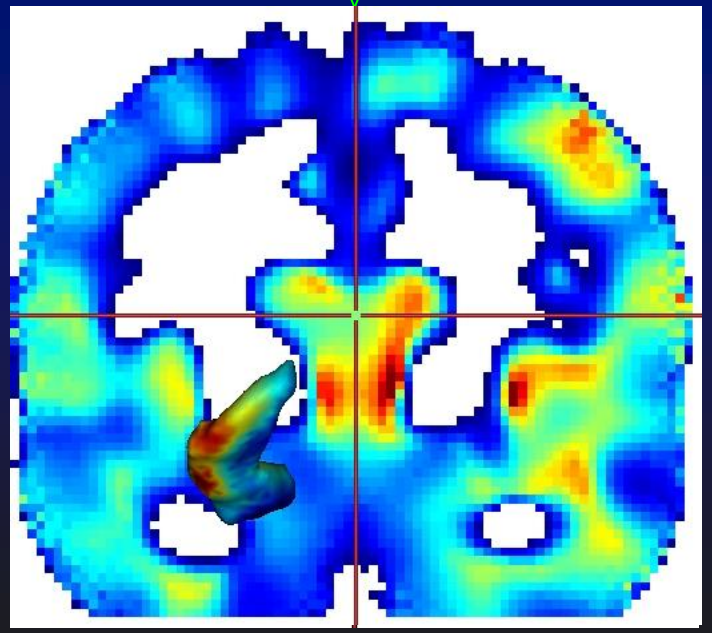
3D hippocampal surface

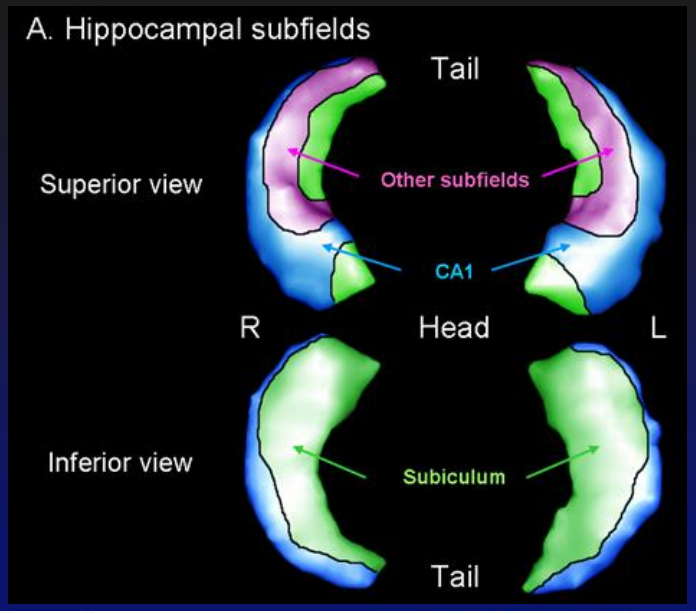


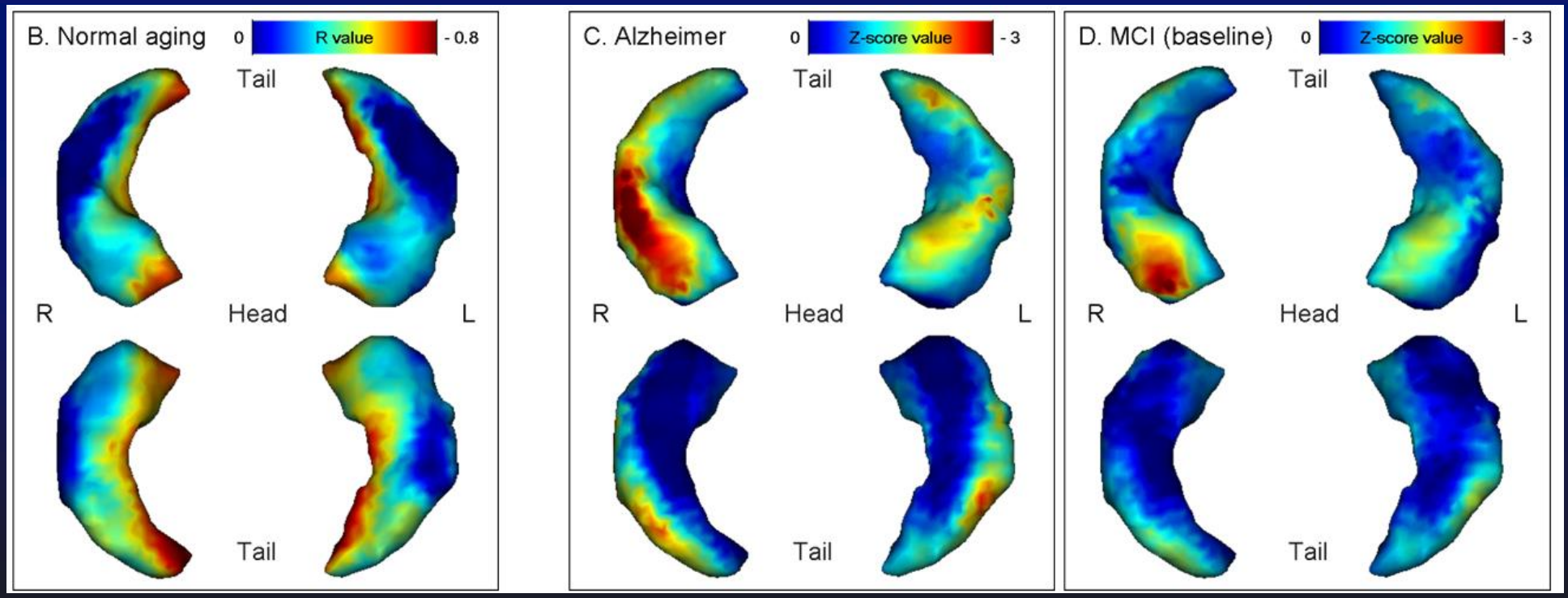
SPM-T map of GM atrophy



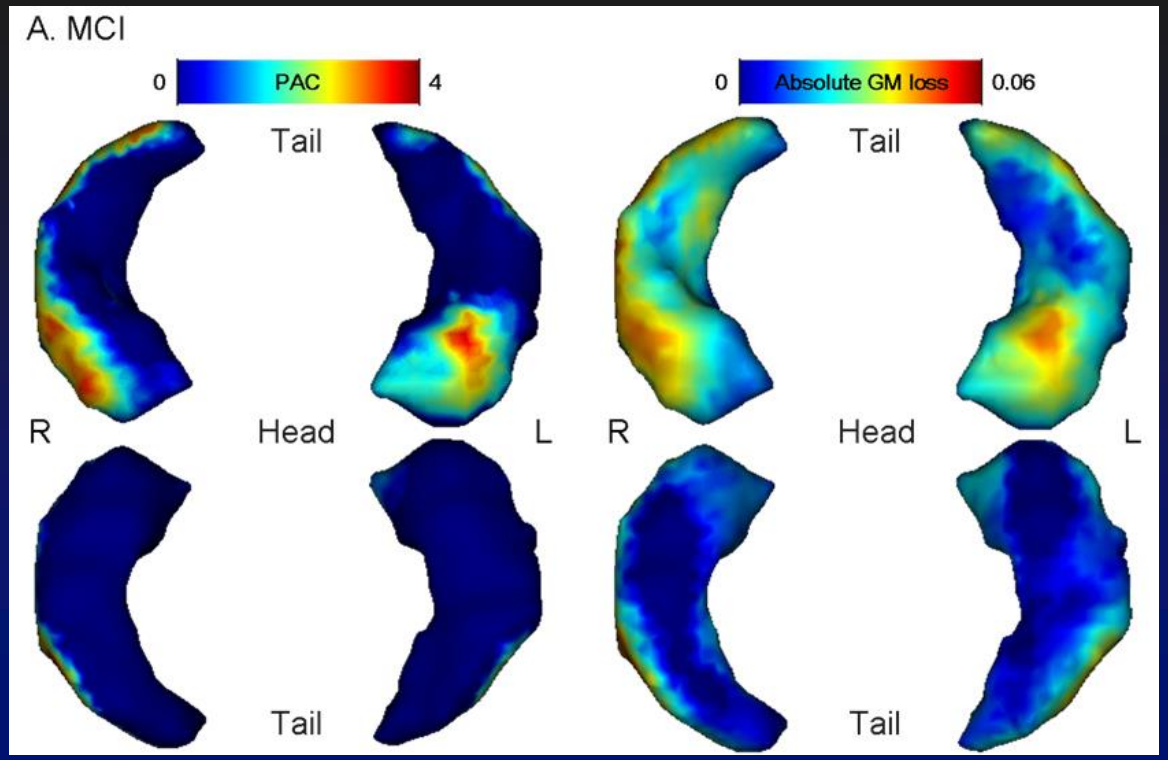
FUSION (ANATOMIST/BRAINVISA)

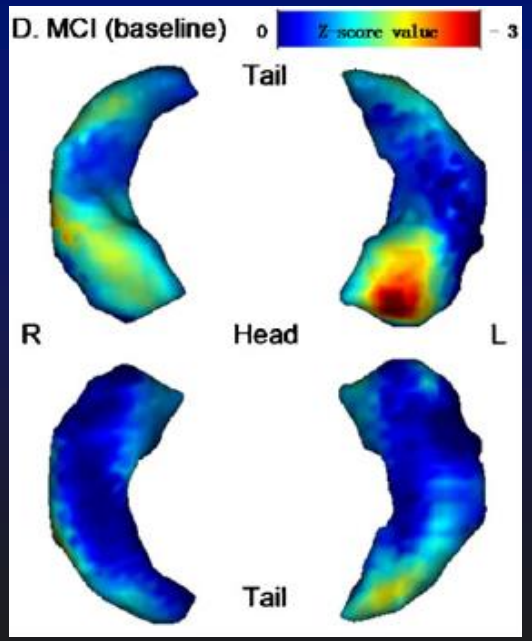


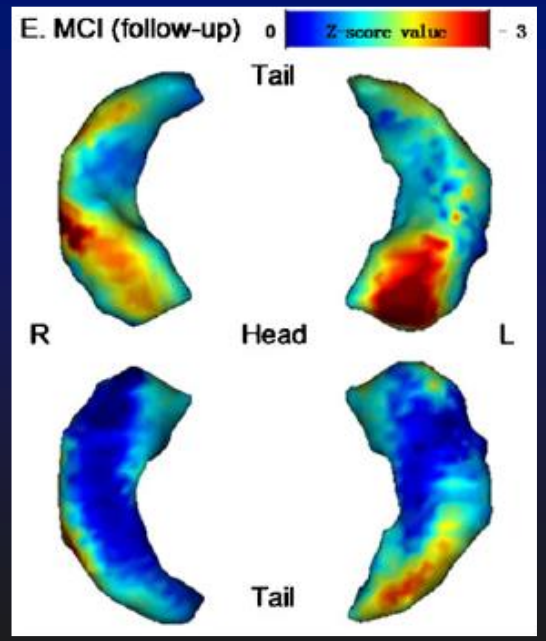




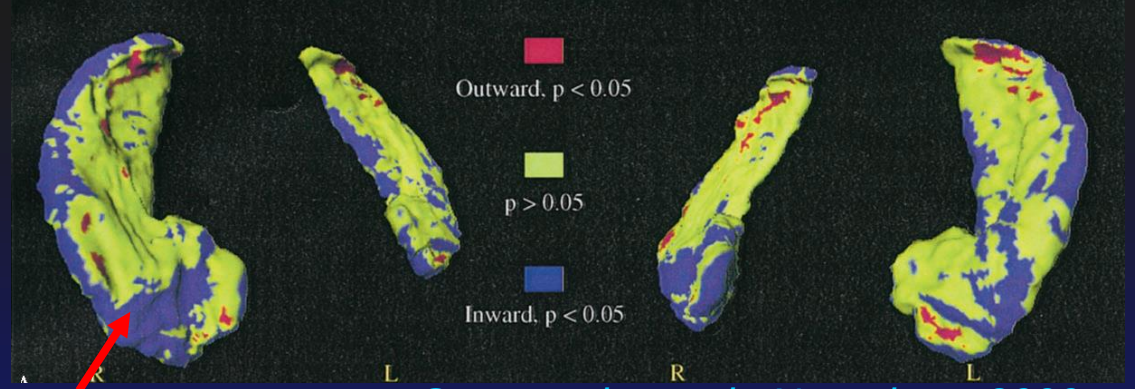
Chételat et al., Neuropsychologia, 2008



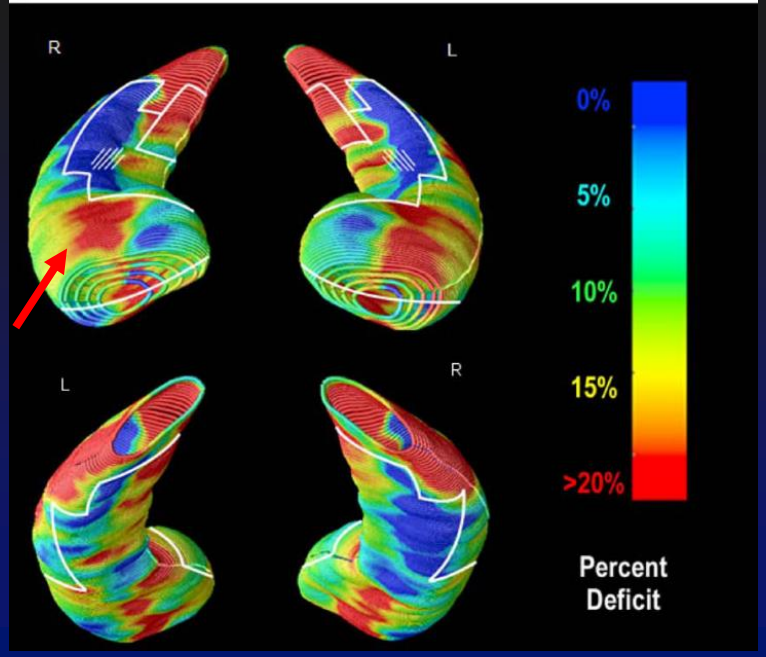




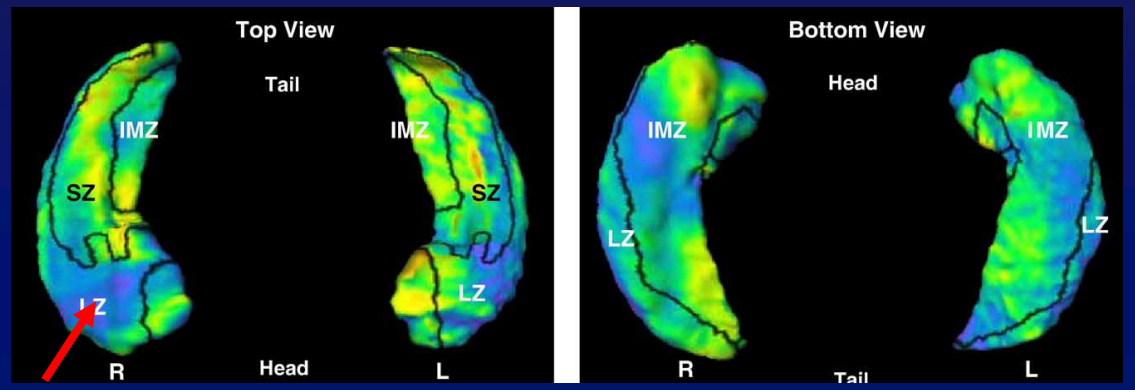
Chételat et al., Neuropsychologia, 2008



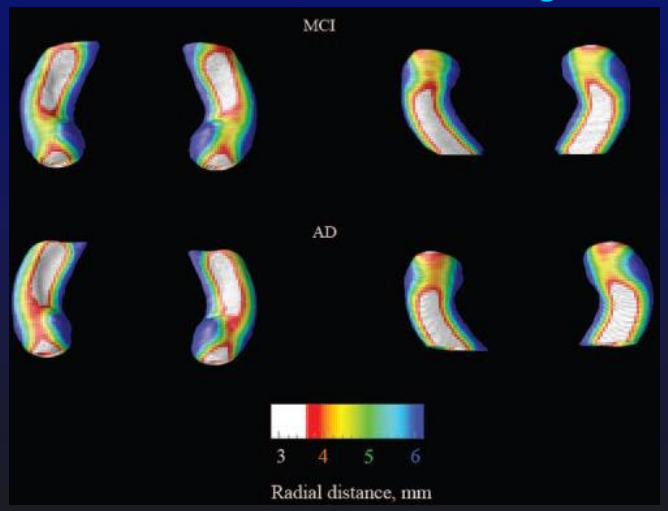
Csernansky et al., Neurology, 2000



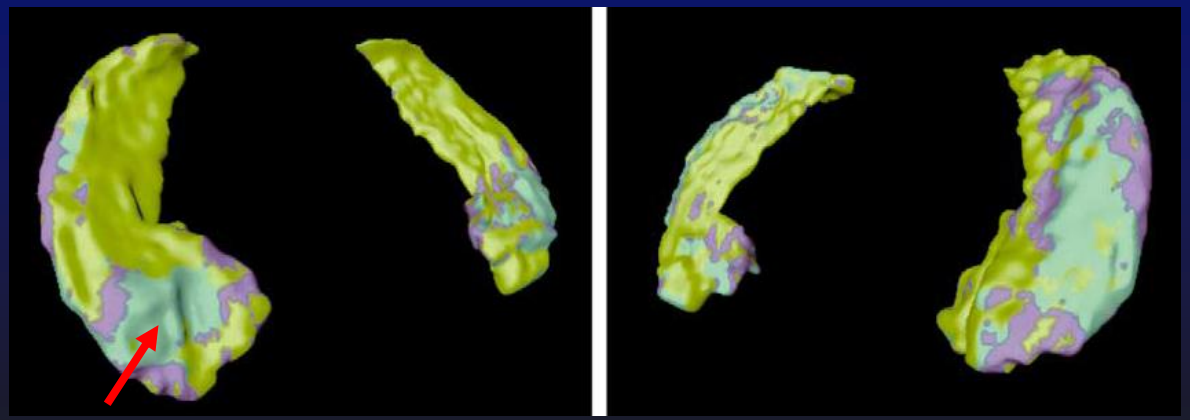
Frisoni et al., Neuroimage, 2006



Wang et al., Neuroimage, 2006



Apostolova et al., Brain, 2006



Wang et al., Neuroimage, 2003

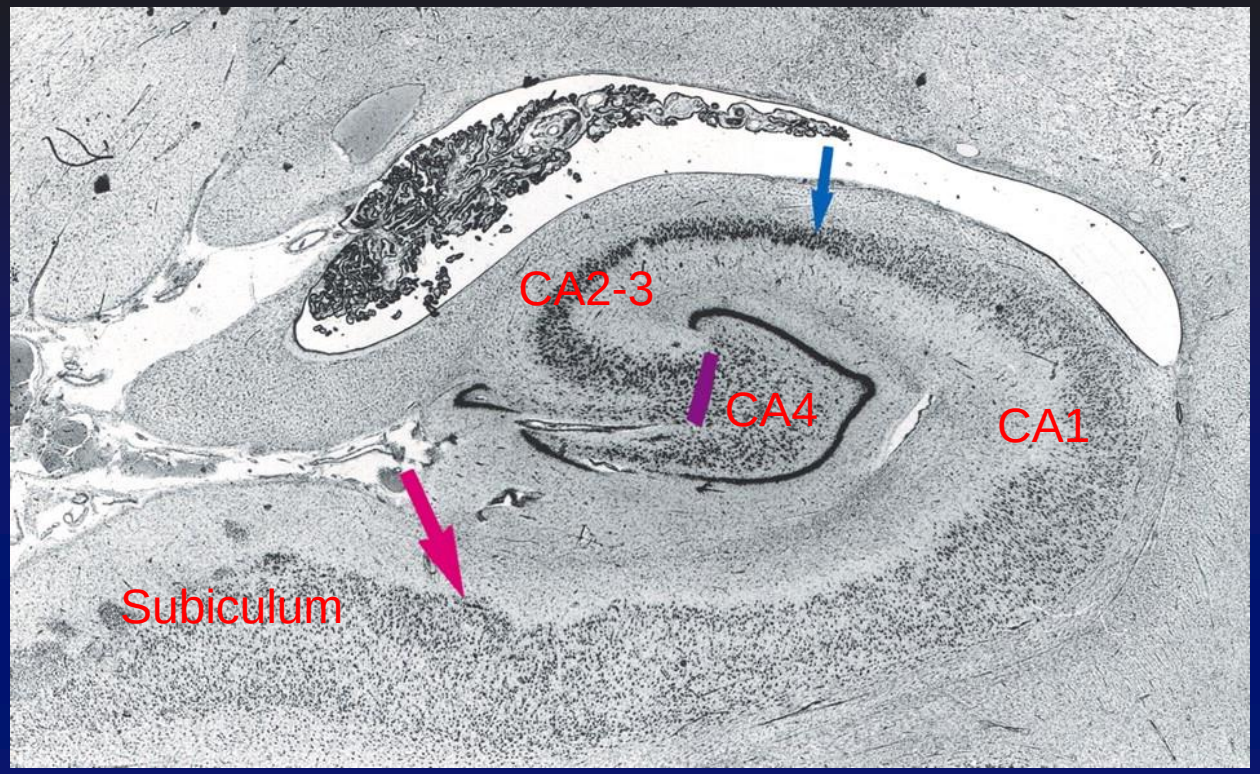
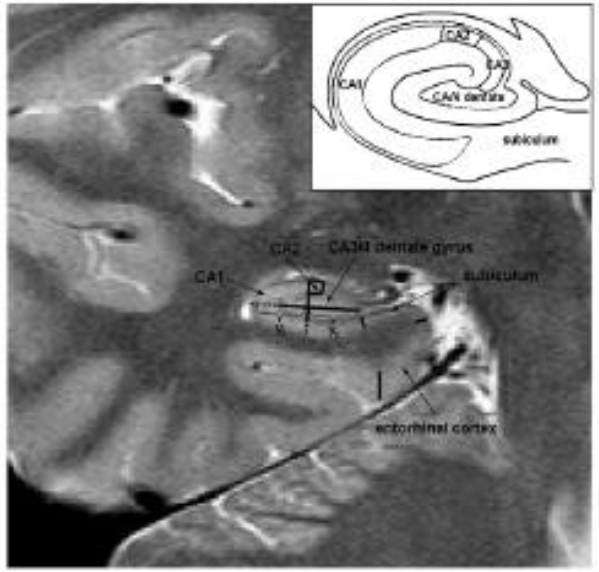


Figure 1.: Transverse Section of the Body of the Hippocampus Showing Divisions Between CA4 and CA3, CA2 and CA1, and CA1 and the Subiculum[a]
[a]The purple bar marks the division between CA4 and CA3. The blue arrow marks the division between CA2 and CA1, and the red arrow marks the division between CA1 and the subiculum. The margin of the subiculum is at the left-hand margin of the figure.

Walker et al., Am J Psychiatry 2002

MRI: high resolution T2 weighted fast spin echo sequence



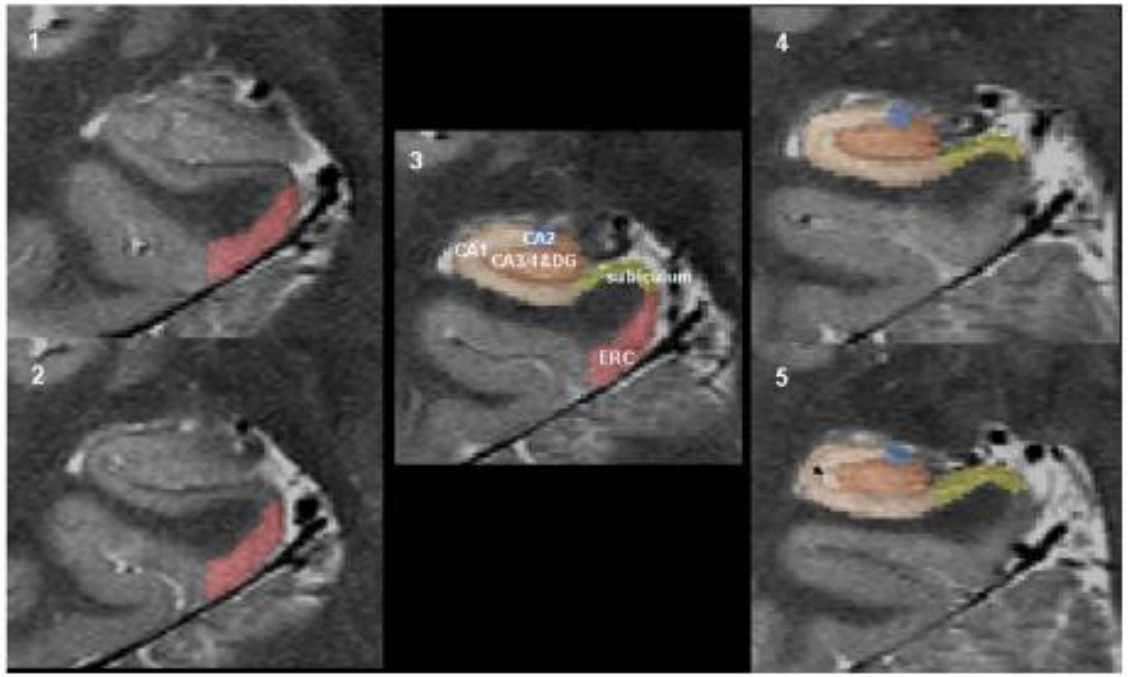
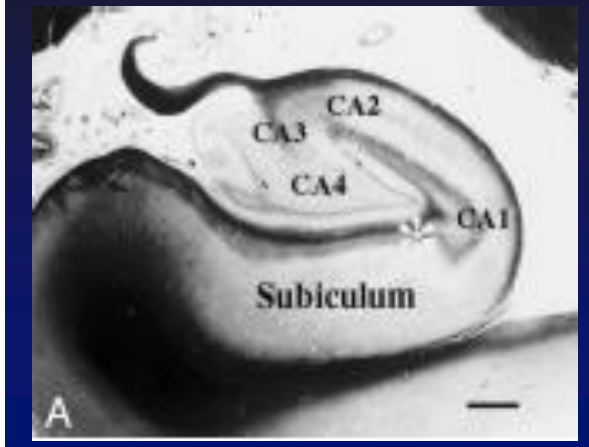


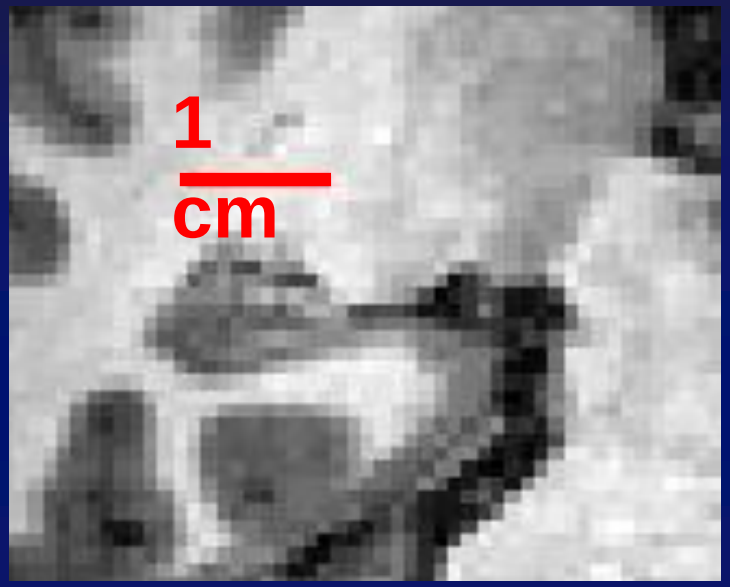
Fig. 2. (a) The marking scheme used in the study. The inset shows a diagram of the hippocampal subfield derived from a histological specimen (adapted from Ref. [5]). As it is not possible to identify individual hippocampal layers at this field strength, the scheme was based on reliably recognizable anatomical landmarks even though this resulted in a part of the prosubiculum and subiculum proper being counted towards the CA1 sector. (b) A typical example of hippocampal subfield markings. No. 1 is the most anterior slice, No. 5 is the most posterior slice. Slice 3 is the referred in the text as "starting" slice. The arrow on slice 5 indicates a cyst in the vestigial hippocampal sulcus which was excluded from the measurement.

Coronal photomicrographs of normal and atrophic hippocampus (Klüver-Barrera stain).



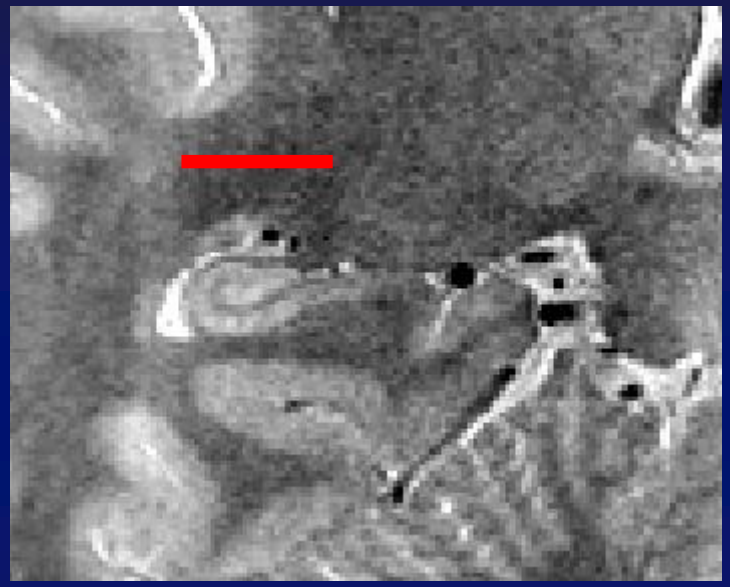
Adachi et al., 2003

Mueller et al., 2007



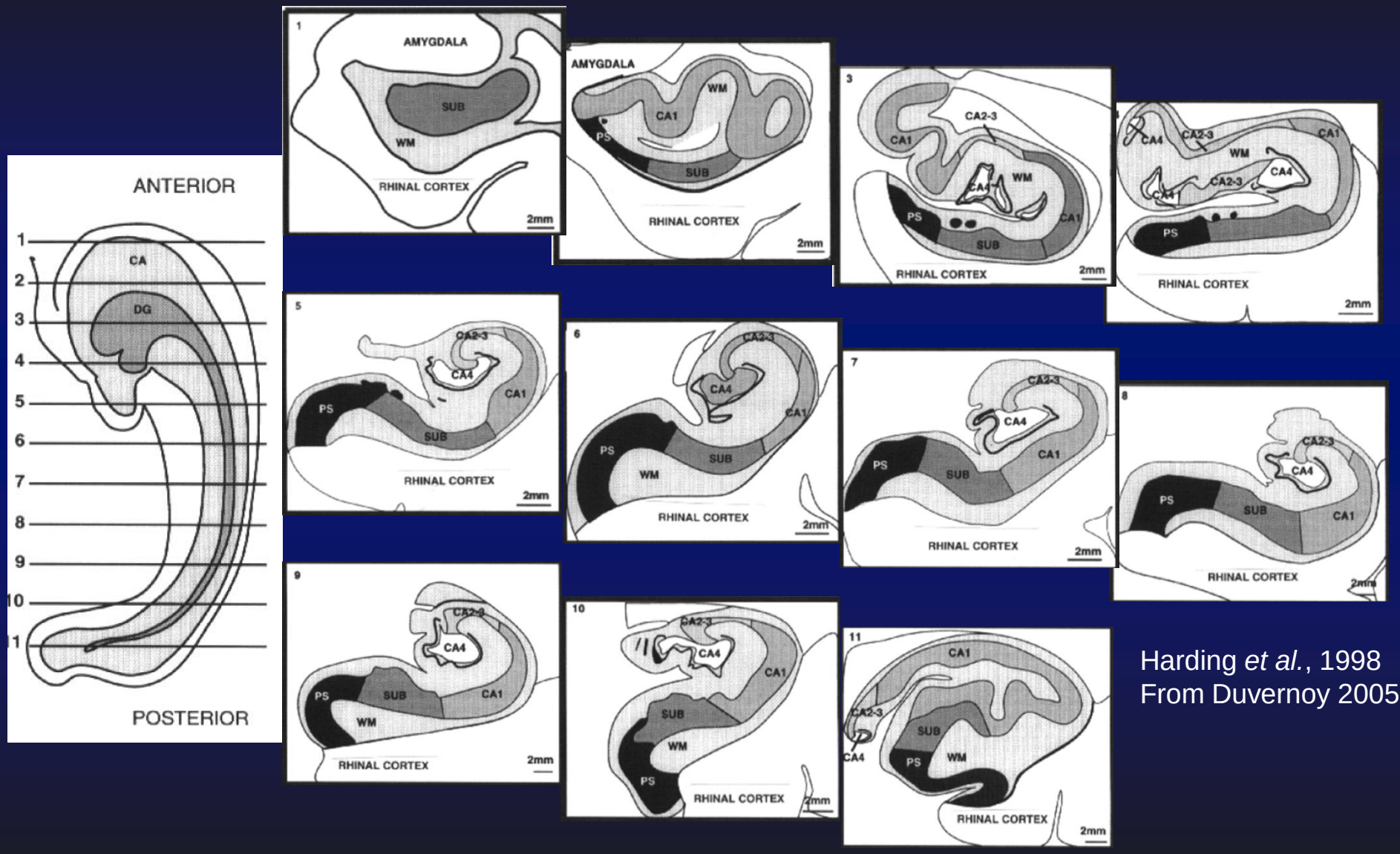
T1 MRI

Resolution = 1 x 1 x 1 mm

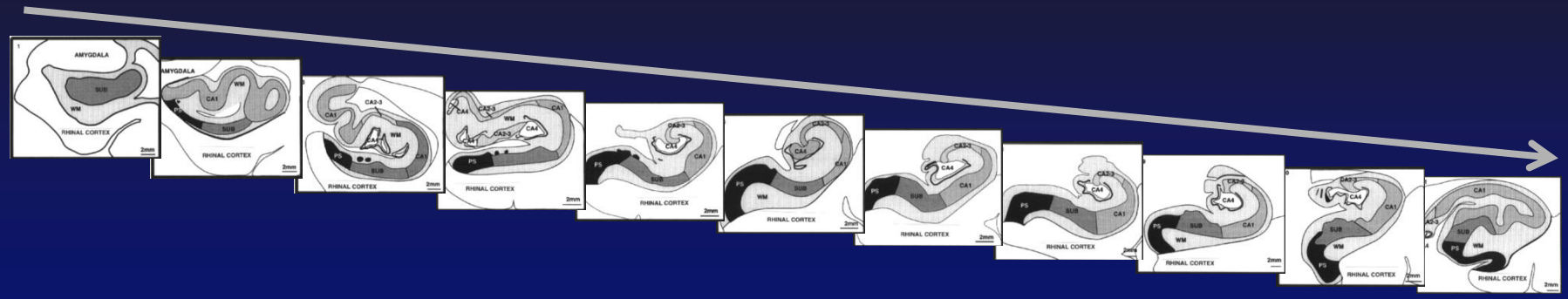


High resolution MRI

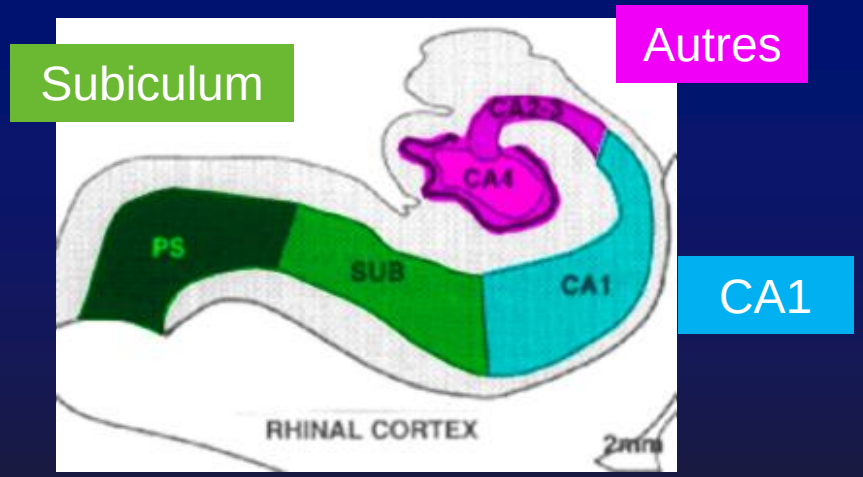
Resolution = 0,375 x 0,375 x 2 mm



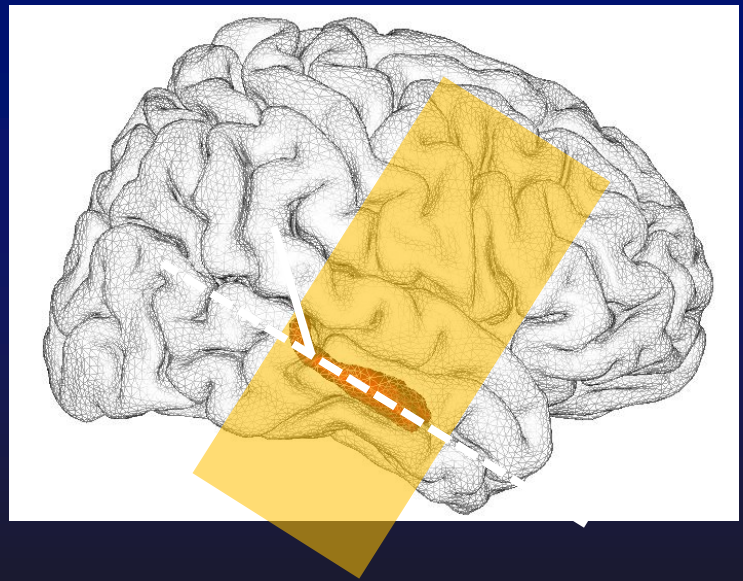
Harding *et al.*, 1998
From Duvernoy 2005

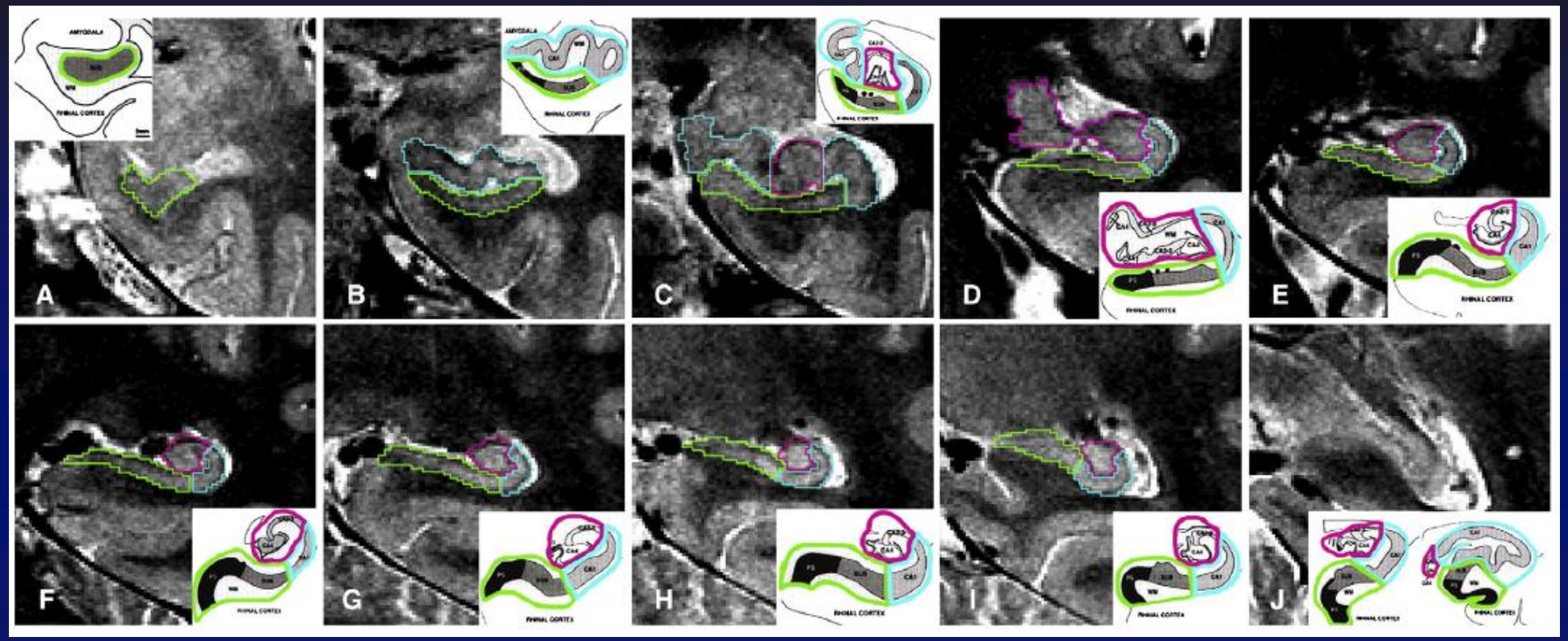


Pooling of regions



Suppression of posterior slices





ICC (intra-class correlation coefficient):

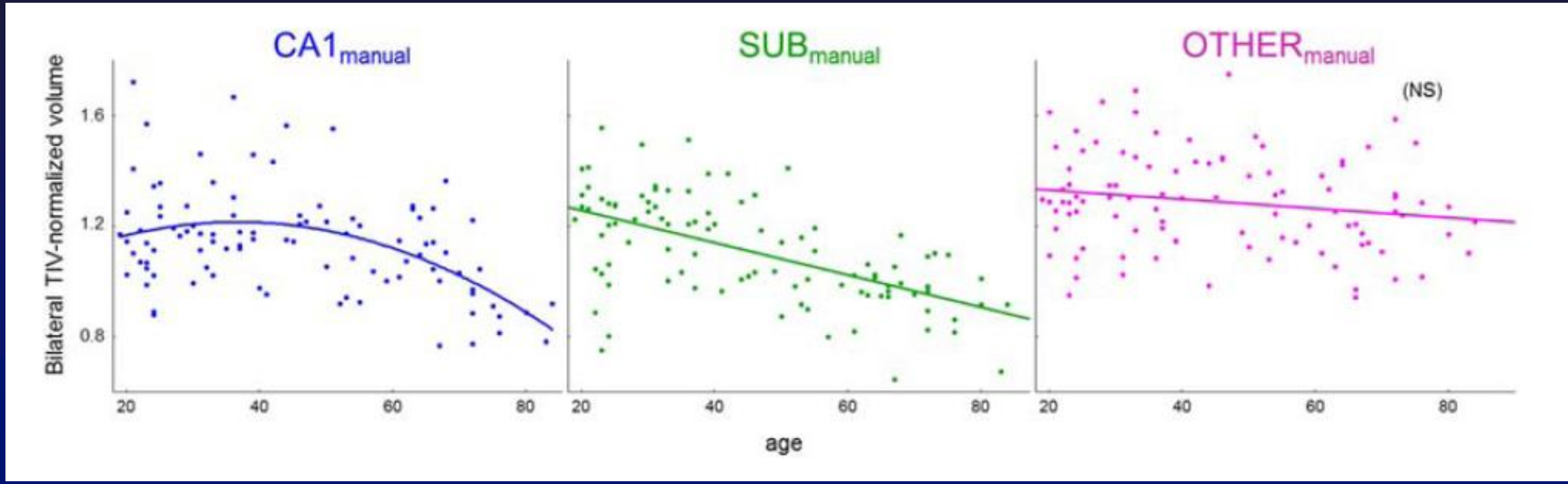
CA1 = 0,94
Subiculum = 0,89
Autre = 0,96

La Joie et al. Neuroimage 2010

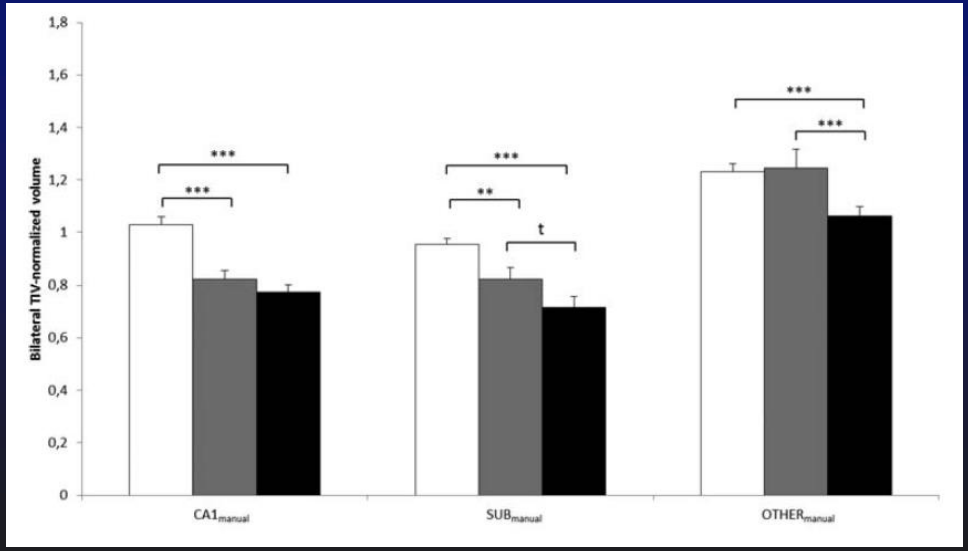
De Flores et al., Cerebral Cortex, 2014

Early diagnosis: hippocampal subfields

Normal aging



Alzheimer's disease



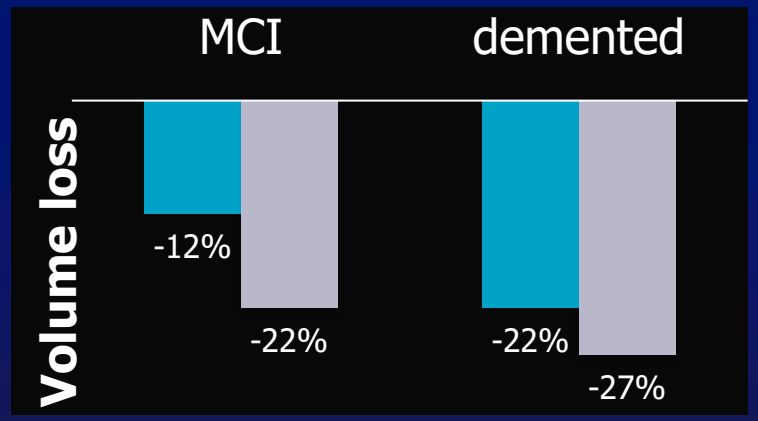
Elderly
MCI
MA

La Joie et al. Neuroimage 2010

De Flores et al., Cerebral Cortex, 2014

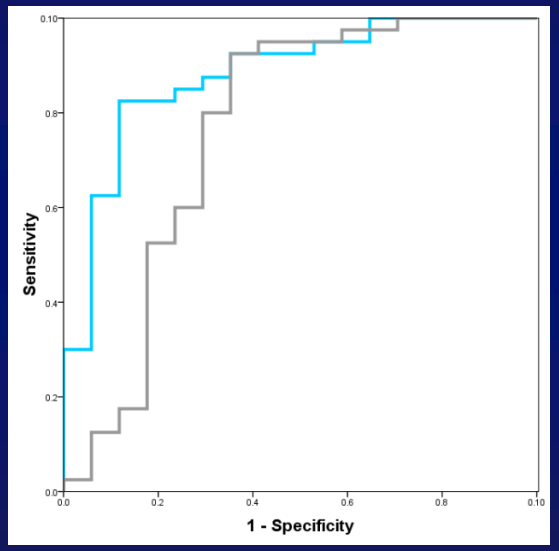
Hippocampal subfield volumetry

CA1 vs total hippocampus



AUC

0,88
vs
0,76



La Joie et al. Neuroimage 2010

De Flores et al., Cerebral Cortex, 2014

HIPPOCAMPAL SUBFIELDS

Towards a unified hippocampal subfield segmentation method



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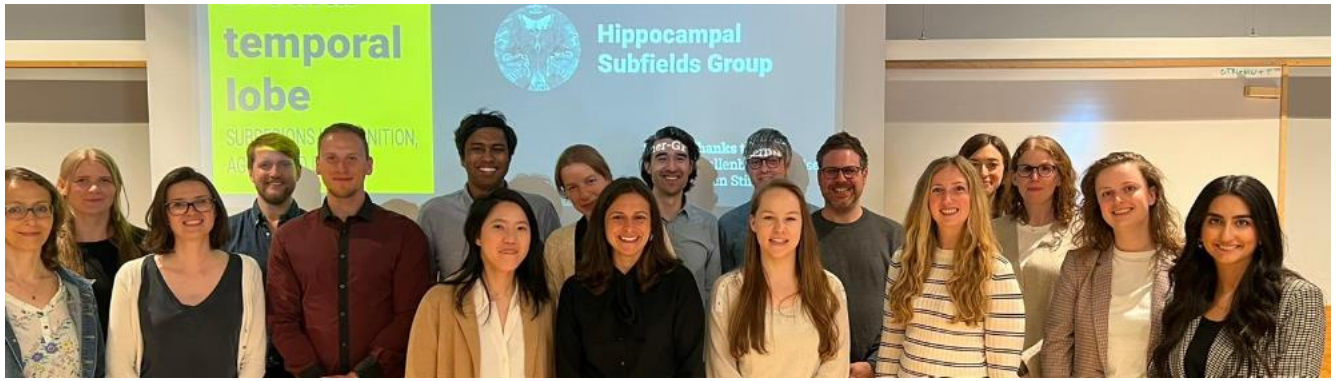
[Hippocampal Subfield Group (@hipposubfields) / Twitter]

//www.hippocampalsubfields.com/



The hippocampus in Alzheimer's disease (AD)

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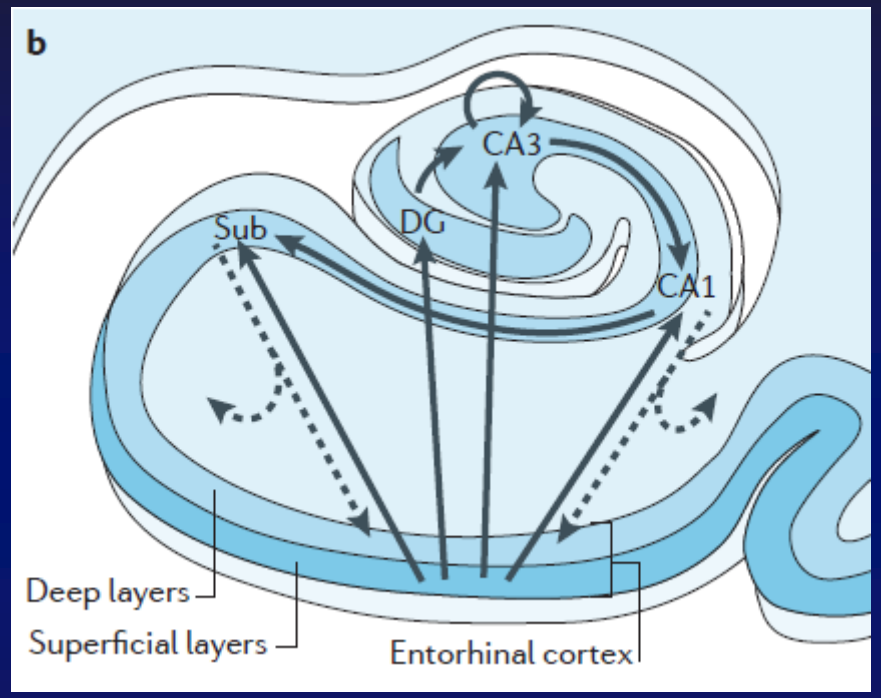


Small et al., 2011

The organization of the hippocampal formation. b | In the hippocampal transverse axis, **superficial layers of the entorhinal cortex** connect with the dentate gyrus (**DG**), **CA3, CA1** and the **subiculum** (Sub). The **trisynaptic circuit** connects the **DG to CA3**, to **CA1** and to the **subiculum**. Through auto-association fibres, **CA3** neurons interconnect with other **CA3** neurons throughout the long axis. The **CA1** and primarily the **subiculum** provide the main hippocampal outflow (shown by dashed arrows), back to the **deep layers of the entorhinal cortex** and also to a range of **cortical and subcortical sites**.

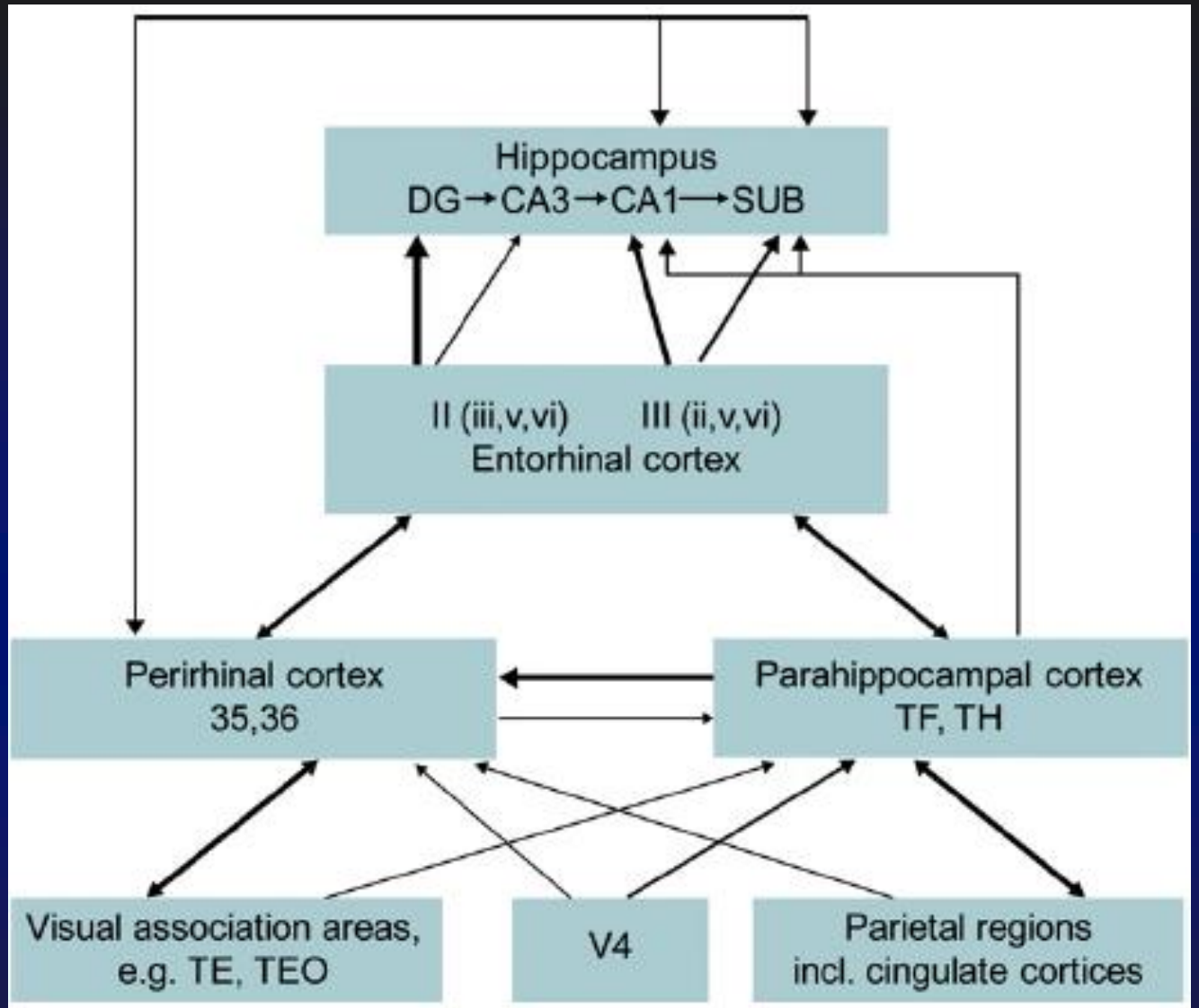
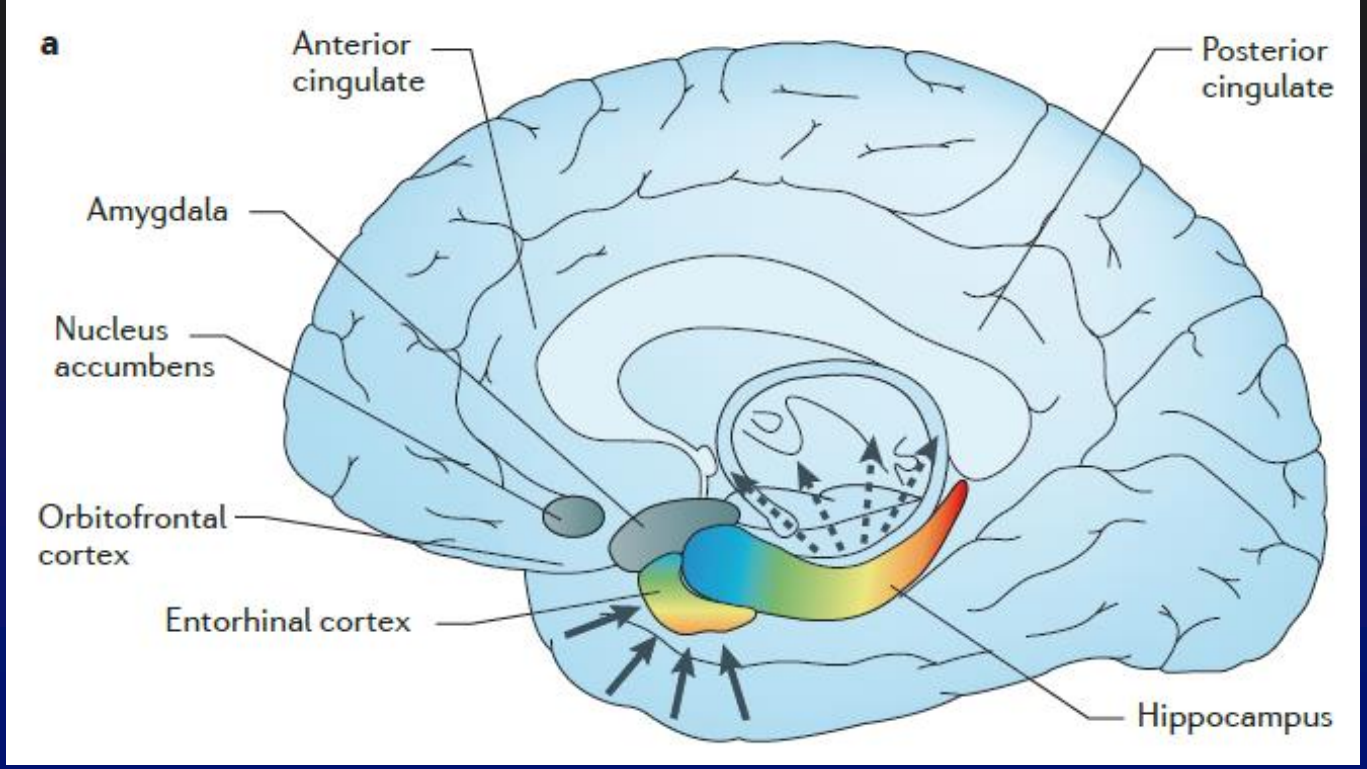


Fig. 1. Schematic diagram of the major interconnections within the primate medial temporal lobe, incorporating the hippocampal subfields (DG, dentate gyrus) and the subiculum (SUB). The targets of the projections from lamina II and III of the entorhinal cortex to the hippocampus are also indicated. The thickness of the arrows reflects the strength of the various connections.

Aggleton, 2011

In addition to its subdivisions in terms of **subfields**, the hippocampus is also subdivided according to its **antero-posterior axis** (Fanselow and Donc, 2010; Small et al., 2011). These segregations are paralleled by a variation of both anatomical (Aggleton, 2011) and functional (assessed with functional fMRI; Kahn et al., 2008; Poppenk and Moscovitch, 2011; Sorg et al;, 2009) hippocampal connectivity along this anterio-posterior axis and according to hippocampal subfields.



The colour gradients reflect the topological input– output relations between the hippocampal formation and other brain areas, as well as its internal functional and molecular organization. Input to the hippocampus is shown by solid arrows, hippocampal outflow is shown by dashed arrows. Cortical and subcortical information funnels onto **superficial layers of the entorhinal cortex**, and **this input is organized in an anterior–medial to posterior– lateral gradient** (shown by the colour gradient in the entorhinal cortex). This anatomical **gradient is largely preserved** as the entorhinal cortex conveys this information to the **hippocampus** (shown by the corresponding colour code in the hippocampus). The long-axis gradient is preserved in the output pattern of the hippocampus. As well as reconnecting with the entorhinal cortex, the hippocampus monosynaptically connects with — **from anterior to posterior — the orbitofrontal cortex, anterior cingulate, amygdala, nucleus accumbens and posterior**

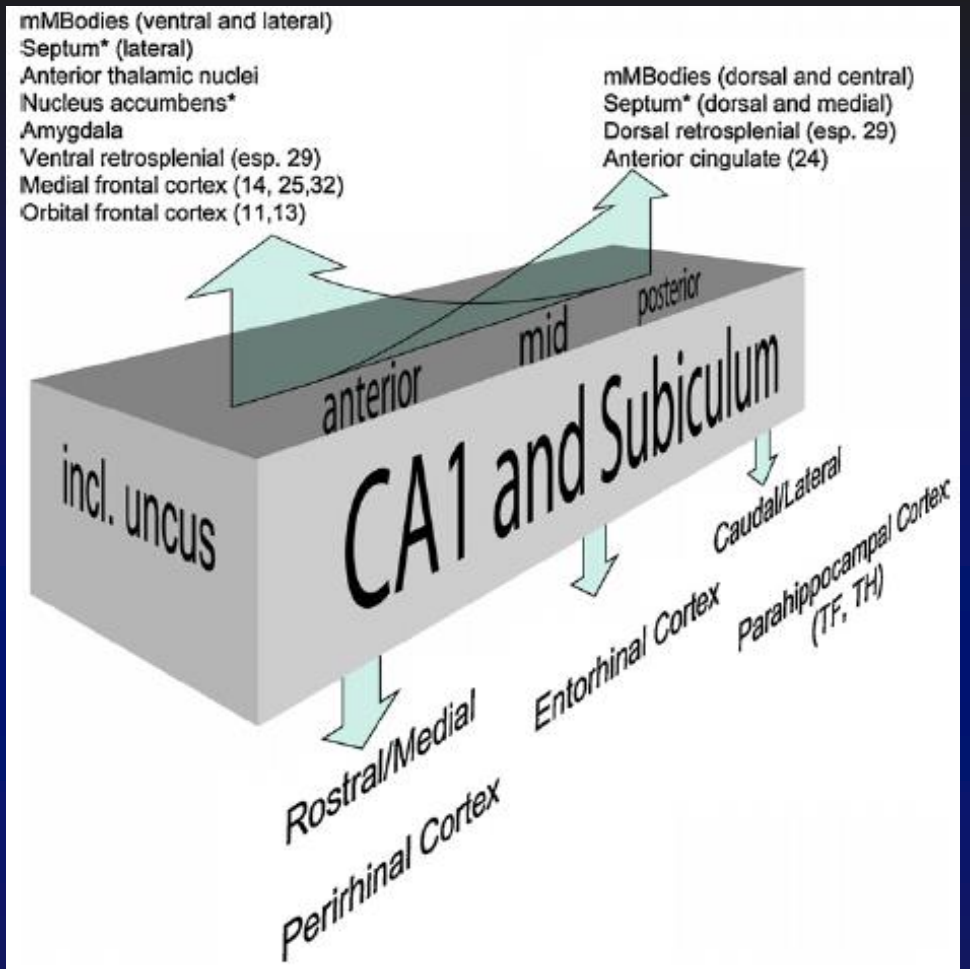
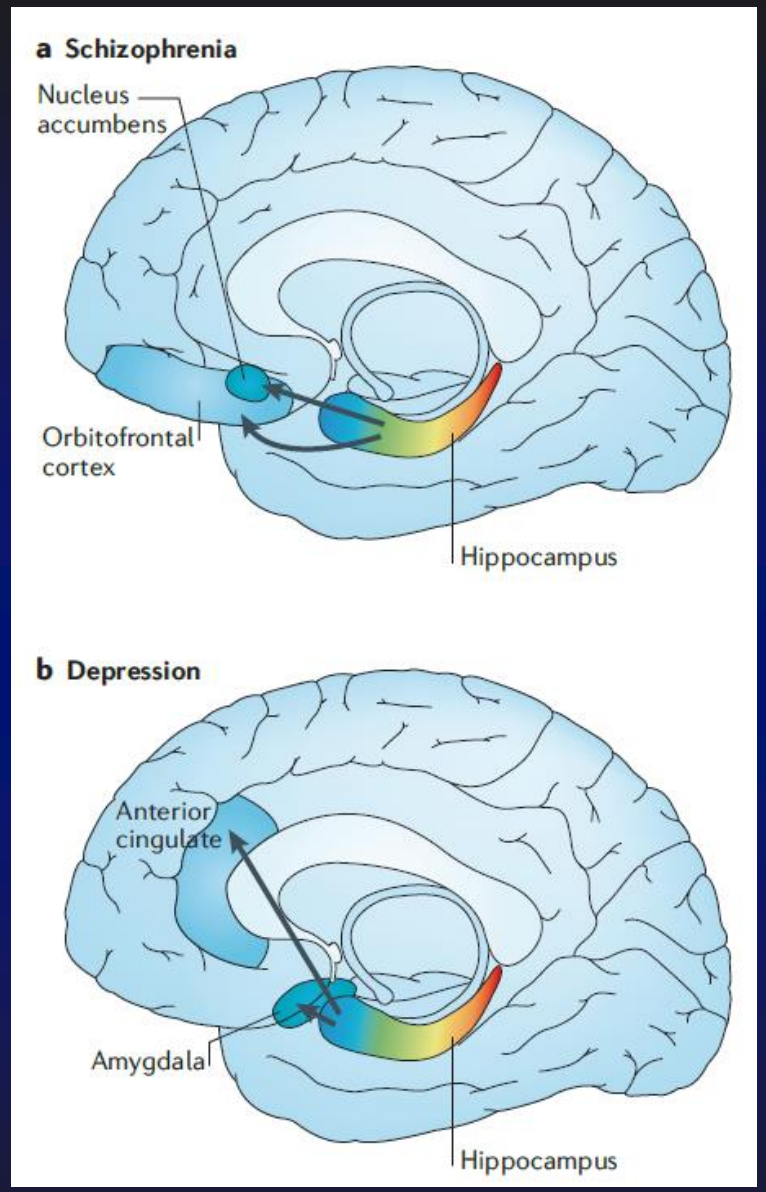


Fig. 2. Schematic diagram showing those hippocampal efferents that arise predominantly from the anterior, mid, or posterior hippocampus (CA1 field and subiculum). Projections to the parahippocampal region are depicted in the lower half of the figure. The numbers refer to area designations. *Abbreviation*: mMBodies, medial nucleus of the mammillary bodies. Asterisks indicate those outputs that also arise from CA3.

Aggleton, 2011



Small et al., 2011

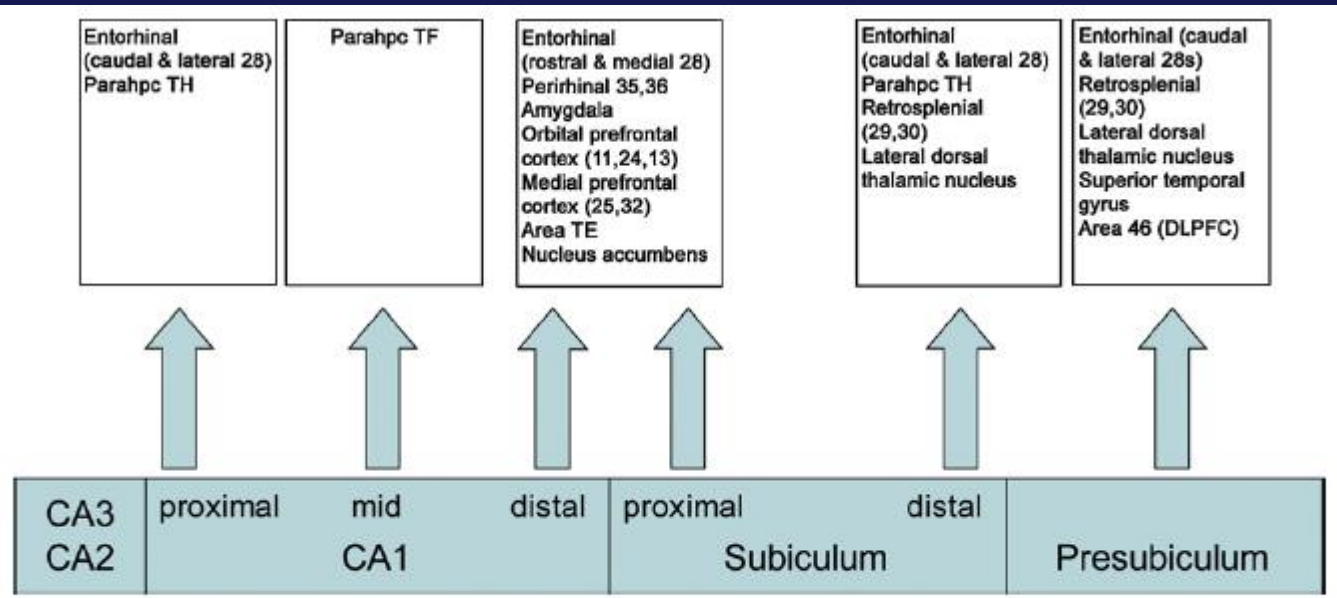


Fig. 4. Schematic diagram showing how different sets of hippocampal projections arise from distinct proximal and distal parts of the CA1 field and subiculum. Projections arising from the presubiculum are also indicated. Note how the efferents from the distal CA1 and proximal subiculum group together, as do many of those from the proximal CA1 and distal subiculum. *Abbreviations*: DLPFC, dorsolateral prefrontal cortex; Parahpc, parahippocampal cortex. The numbers correspond to cortical area designations.

Resting-state functional connectivity of hippocampal subfields

Image acquisition

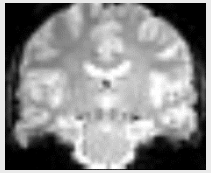
3T Philips MRI camera

Resting-state functional sequence

RT = 2382 ms ; ET = 30 ms ; Flip angle = 80°

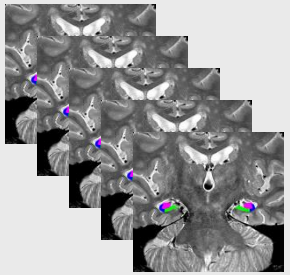
Resolution = 2.8 x 2.8 x 2.8 mm

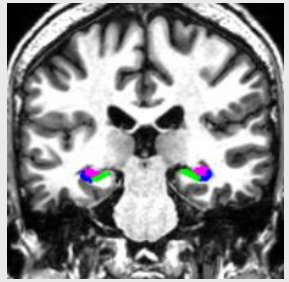
280 volumes



Anatomical seeds

Manual delineations (50 HC)

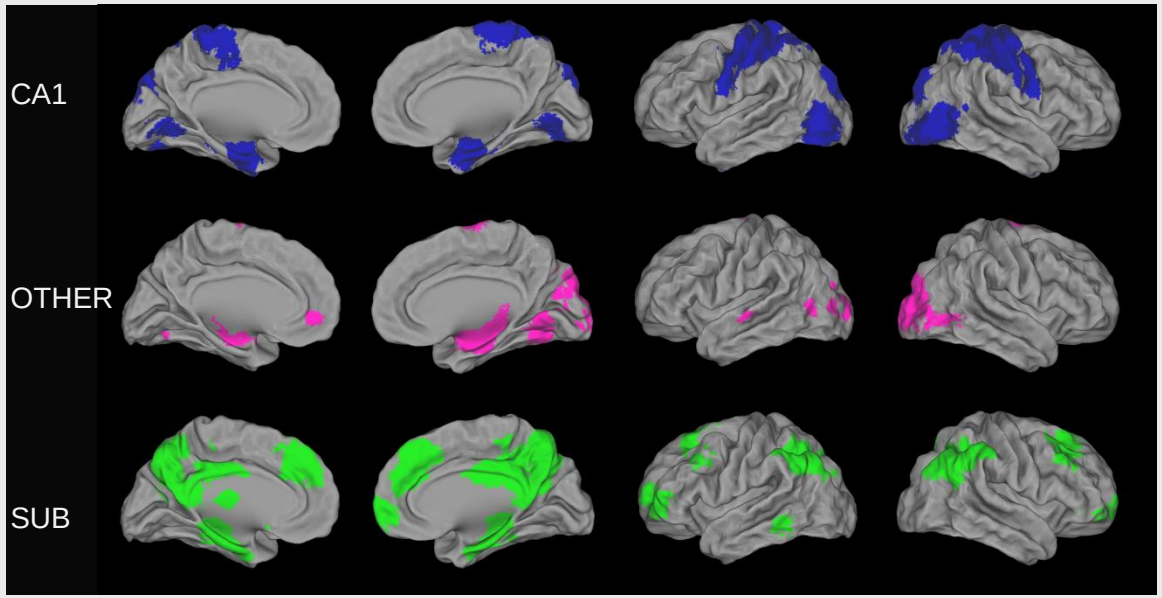




Warped (MNI space)
+ averaged

Connectivity maps

36 healthy controls (aged 68.5 ± 5.7), AV-45 negative



De Flores et al., 2017

Neurofunctional Topography of the Human Hippocampus

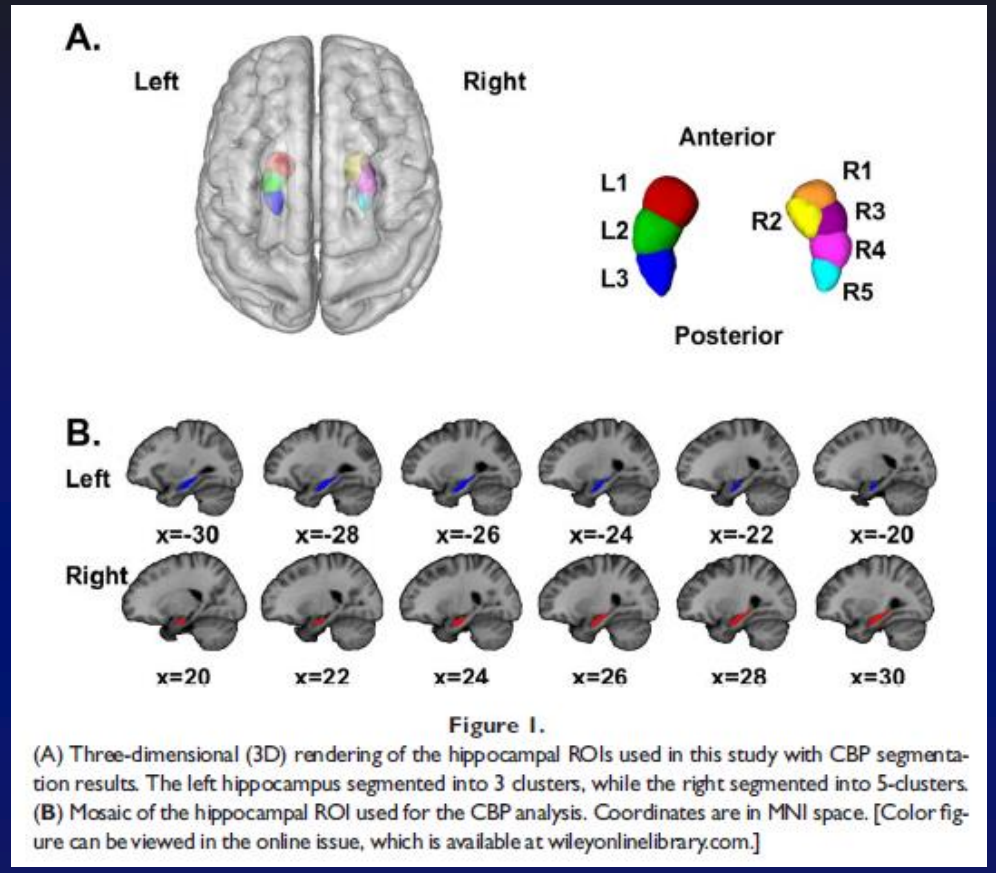
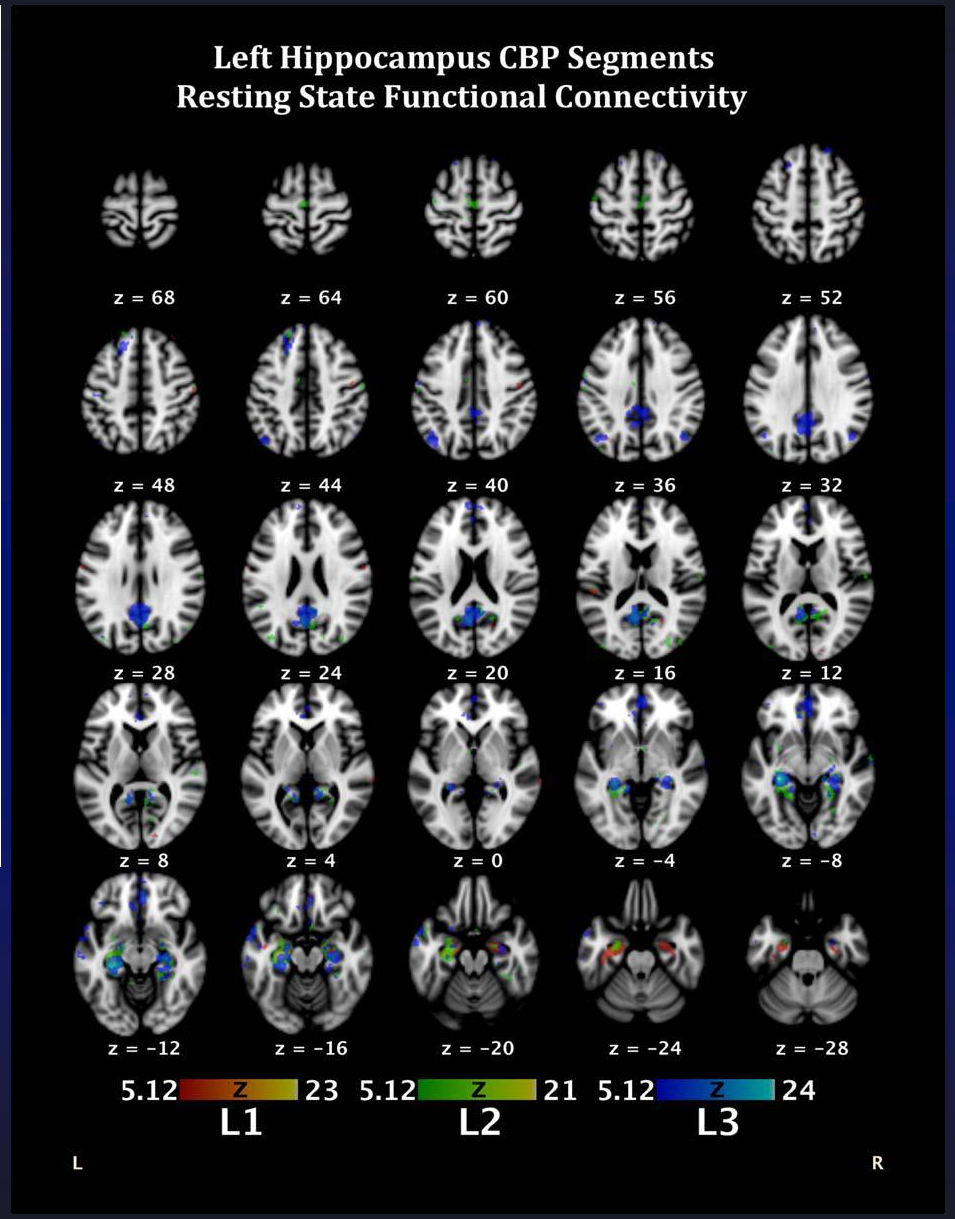


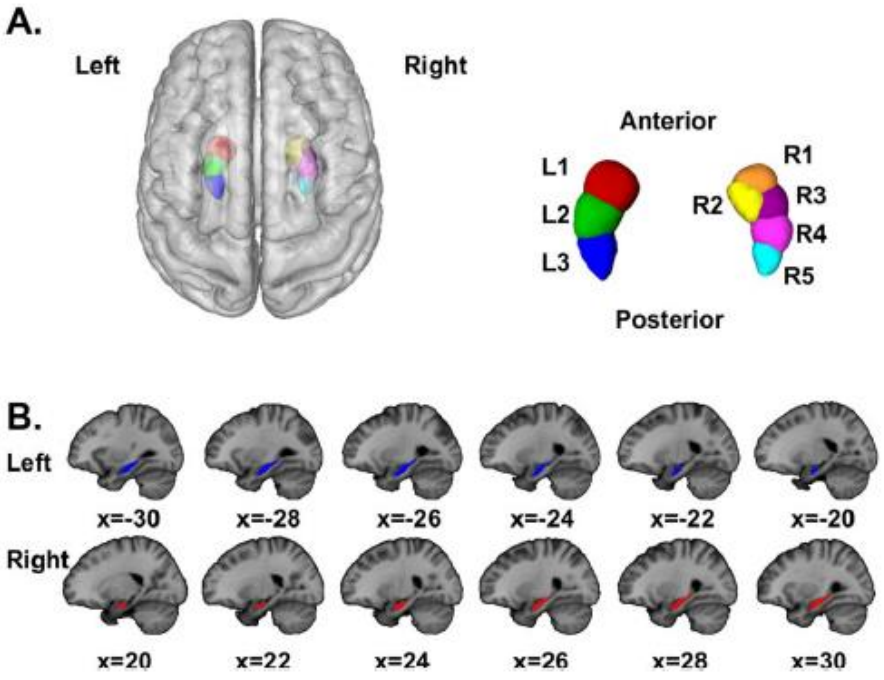
Figure 1.

(A) Three-dimensional (3D) rendering of the hippocampal ROIs used in this study with CBP segmentation results. The left hippocampus segmented into 3 clusters, while the right segmented into 5-clusters. (**B**) Mosaic of the hippocampal ROI used for the CBP analysis. Coordinates are in MNI space. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



Robinson et al., 2015

Neurofunctional Topography of the Human Hippocampus



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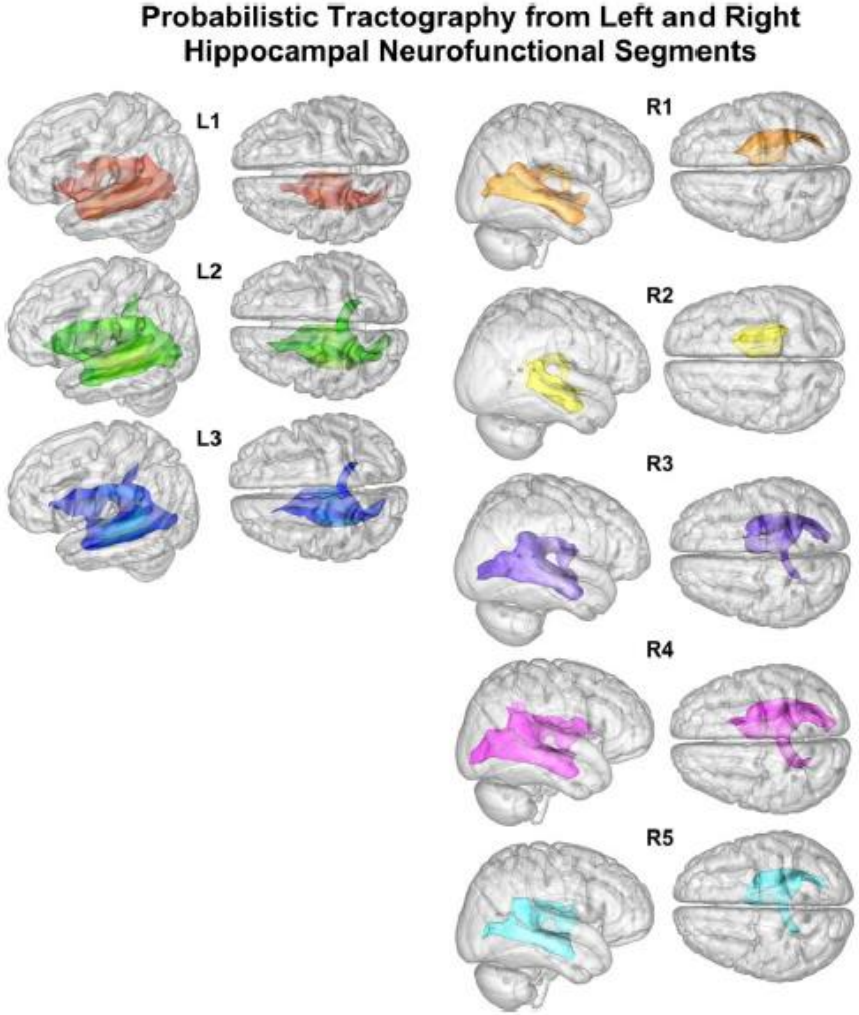


Figure 6.

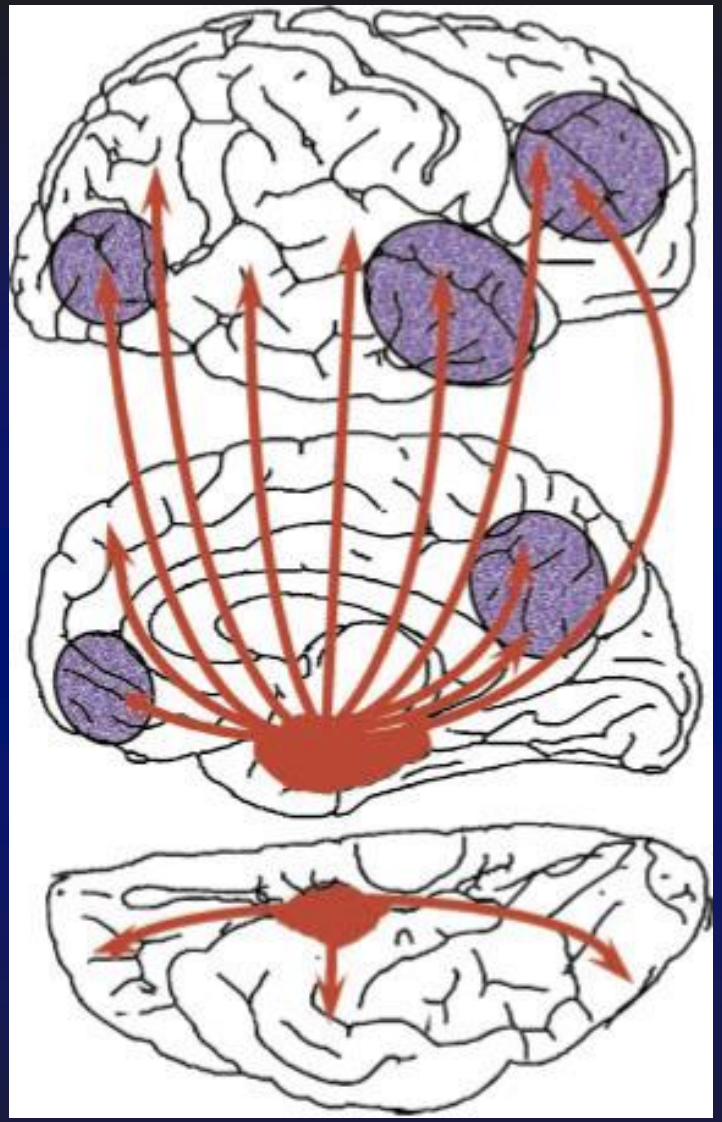
Diffusion tensor imaging (DTI) probabilistic tractography of the left and right hippocampus. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Robinson et al., 2015

The hippocampus in Alzheimer's disease (AD)

1) Introduction: epidemiology, neuropathology and clinical diagnosis
2) Neuroimaging techniques and new criteria
3) Profile of atrophy in AD: from regions-of-interest to voxelwise analyses
4) A differential effect of AD on hippocampal subfields
5) Hippocampal circuitry and connectivity
6) **Beyond the hippocampus: hippocampal networks**

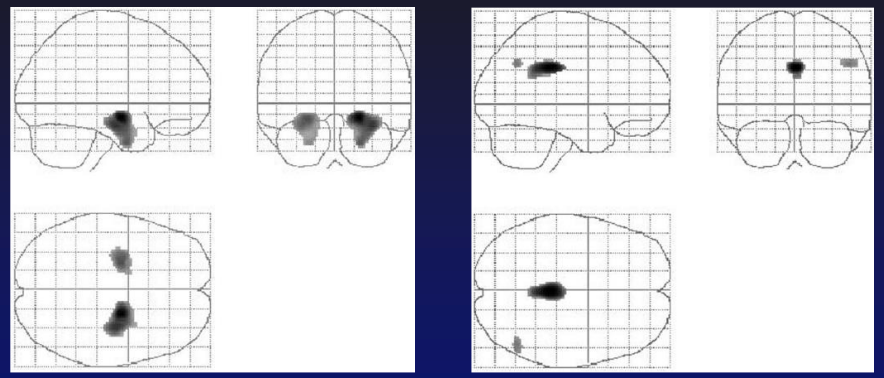
Within the hippocampus, neuronal loss and NFT preferentially concern projection neurons in the CA1 subfield and the subiculum (Arnold *et al., 1991; Braak et al., 2006; Hyman et al., 1984; Pearson et al., 1985*), i.e. neurons that send efferences to numerous cortical areas. These observations have led neuropathologists to propose the hypothesis that these lesions alter hippocampal connectivity, isolating this structure from the rest of the brain *(Hyman et al., 1984).*



Smith, 2002

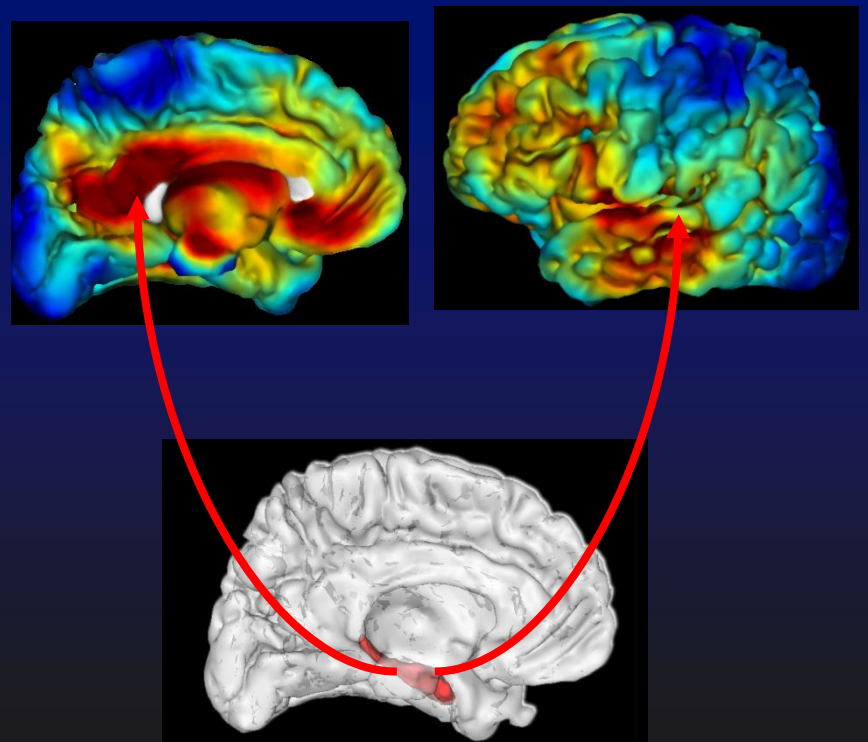
DISCORDANCES Hypometabolism ↔ Atrophy

AD *(Ishii et al., 2005)*



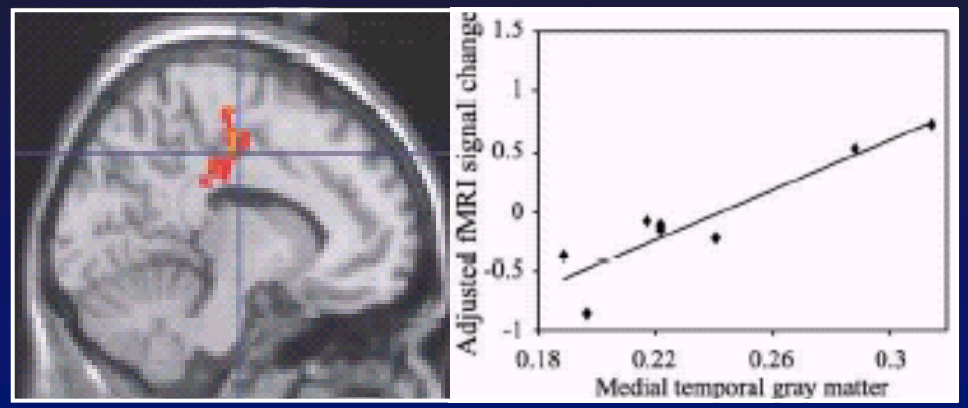
DISCONNECTION HYPOTHESIS

Minoshima et al., 1997; Matsuda, 2001;
Chételat et al., 2003; Nestor et al., 2003



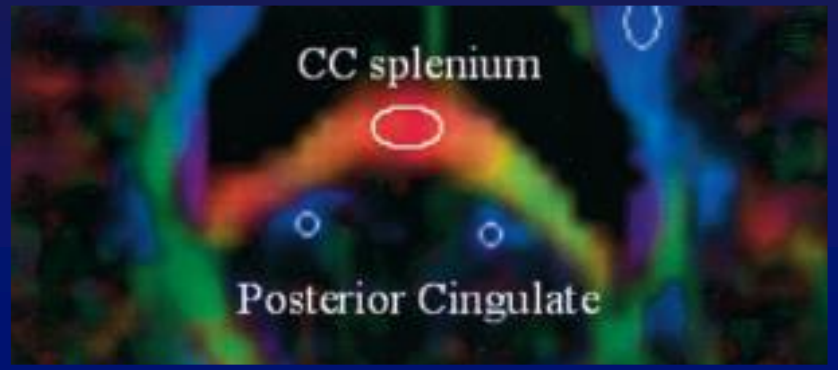
Correlation between hippocampus size and:

- PCC activity (fMRI/memory)



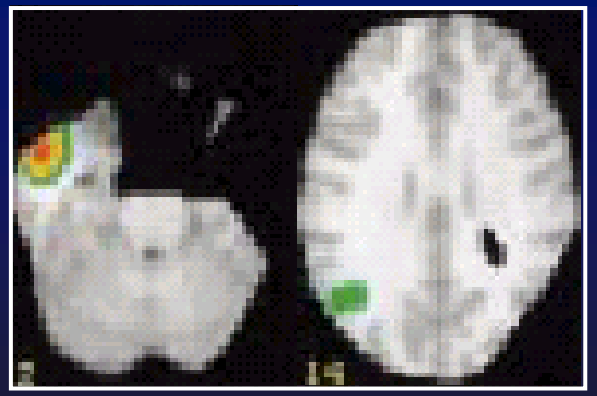
Rémy et al., NeuroImage, 2004

Alteration of cingulum (connect the hippocampus to the PCC)

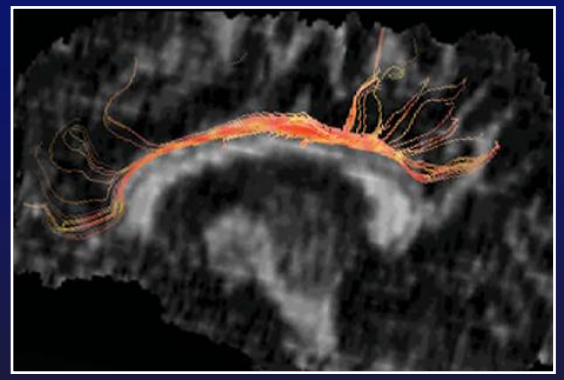


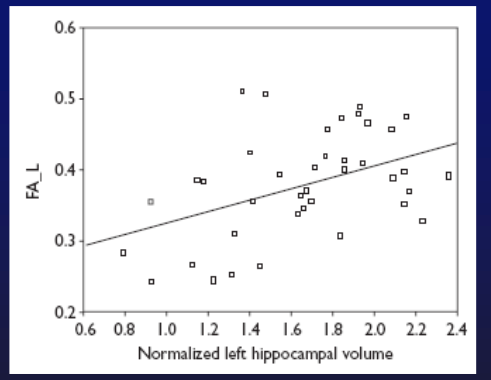
Zhang et al., Neurology, 2007

- Posterior associative cortex hypometabolism



Meguro et al., JNNP, 2001

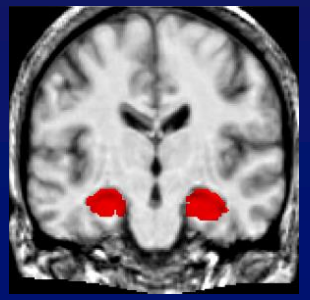




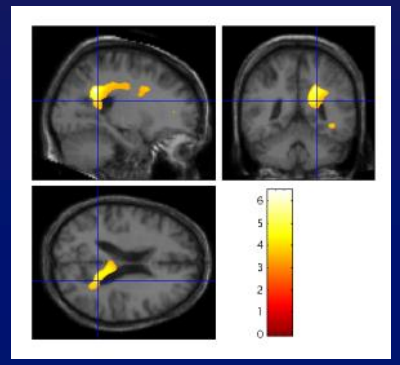
Xie et al., Neurology, 2005

DISCONNECTION / DIASCHISIS HYPOTHESIS: evidence for a link between 1) hippocampal atrophy 2) cingulum disruption and 3) posterior cingulate hypometabolism in Alzheimer's disease (AD)

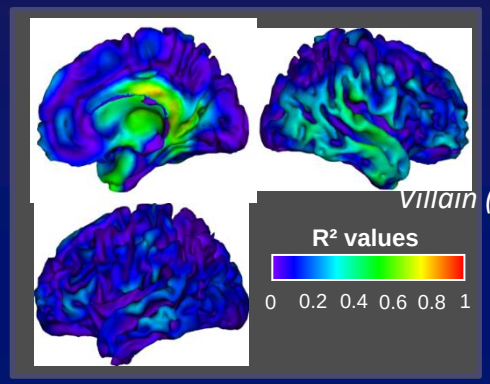
Hippocampal atrophy



Cingulum bundle disruption



Hypometabolism

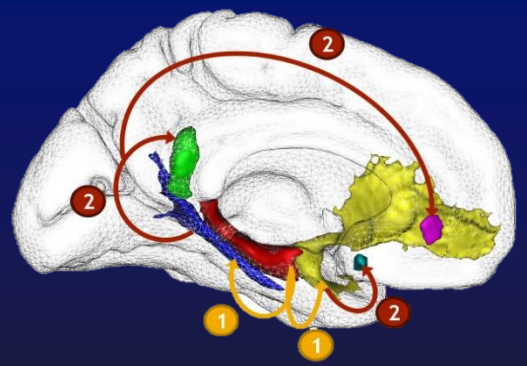


Villain (…) Chételat, J Neurosci 2008

CORRELATION

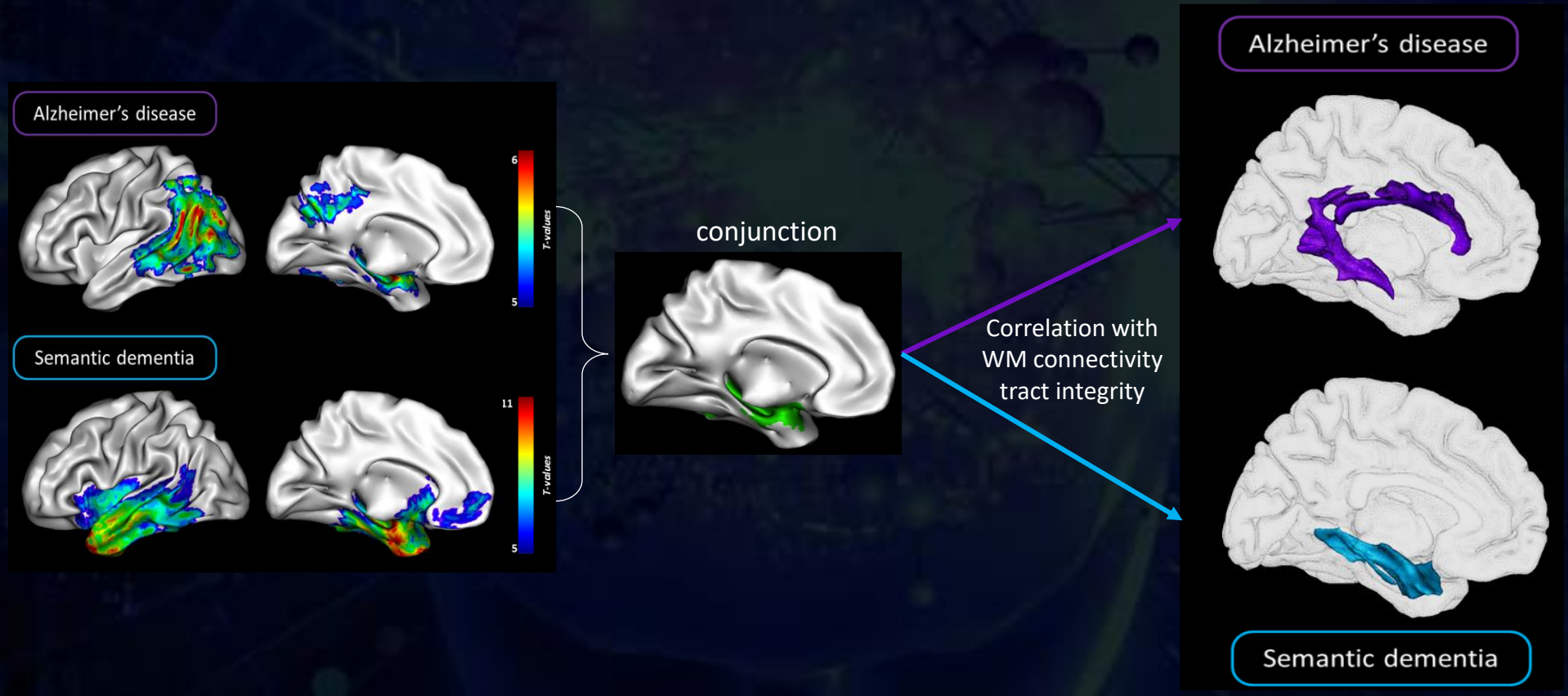
CORRELATION

Minoshima et al., 1997; Matsuda, 2001; Chételat et al., 2003; Nestor et al., 2003



Villain (…) Chételat, Brain, 2010

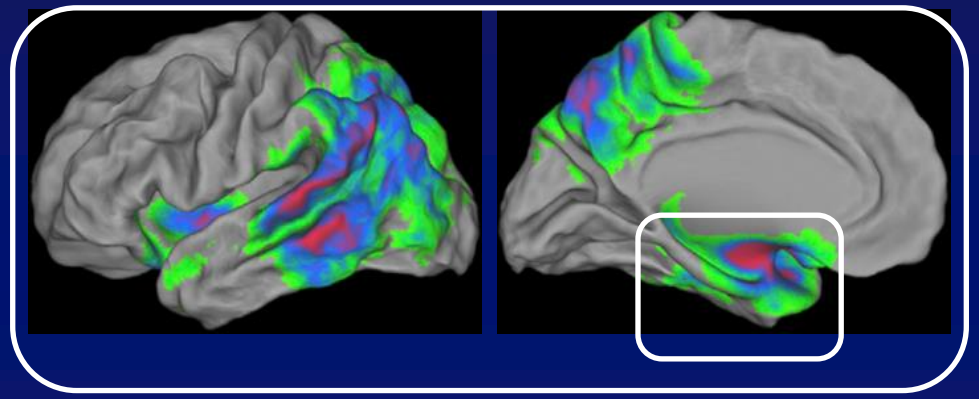
DISCONNECTION: comparison between AD and semantic dementia (SD)



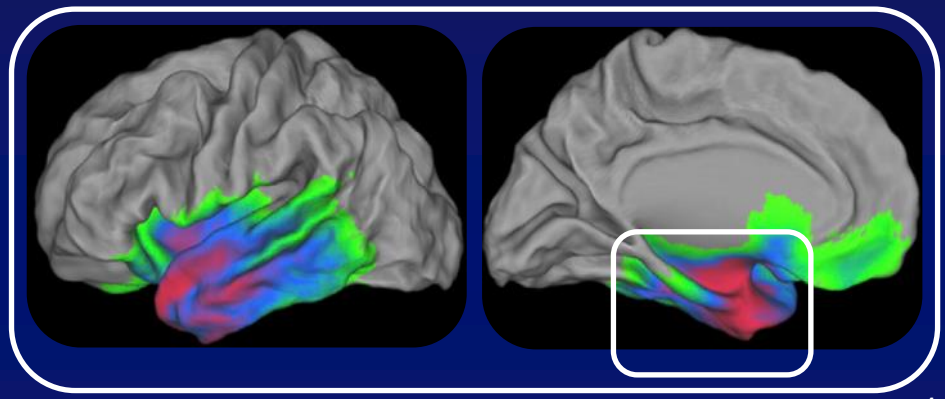
Bejanin (…) Chételat, Cerebral Cortex 2017

Alzheimer's versus semantic dementia:
Two different clinical syndroms

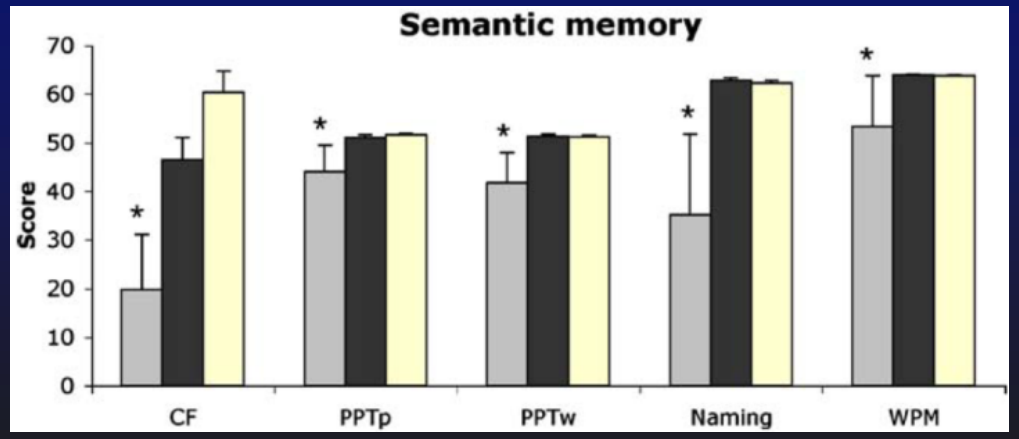
Alzheimer's Disease (AD)

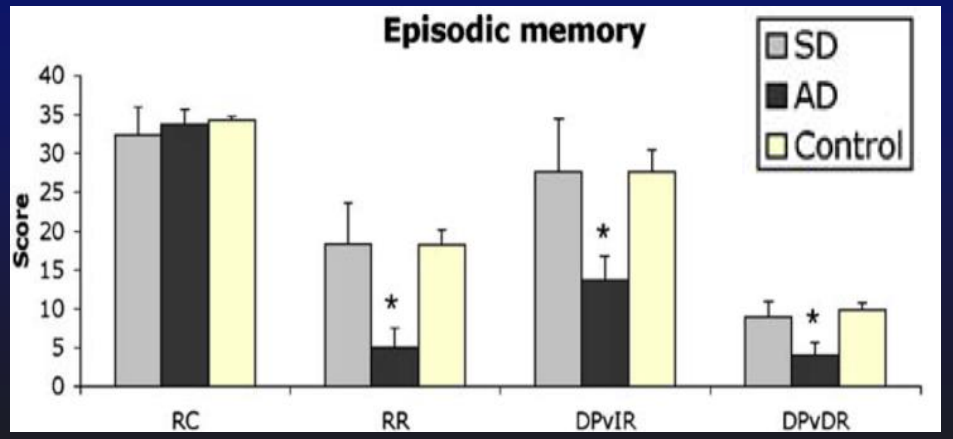


Semantic Dementia (SD)

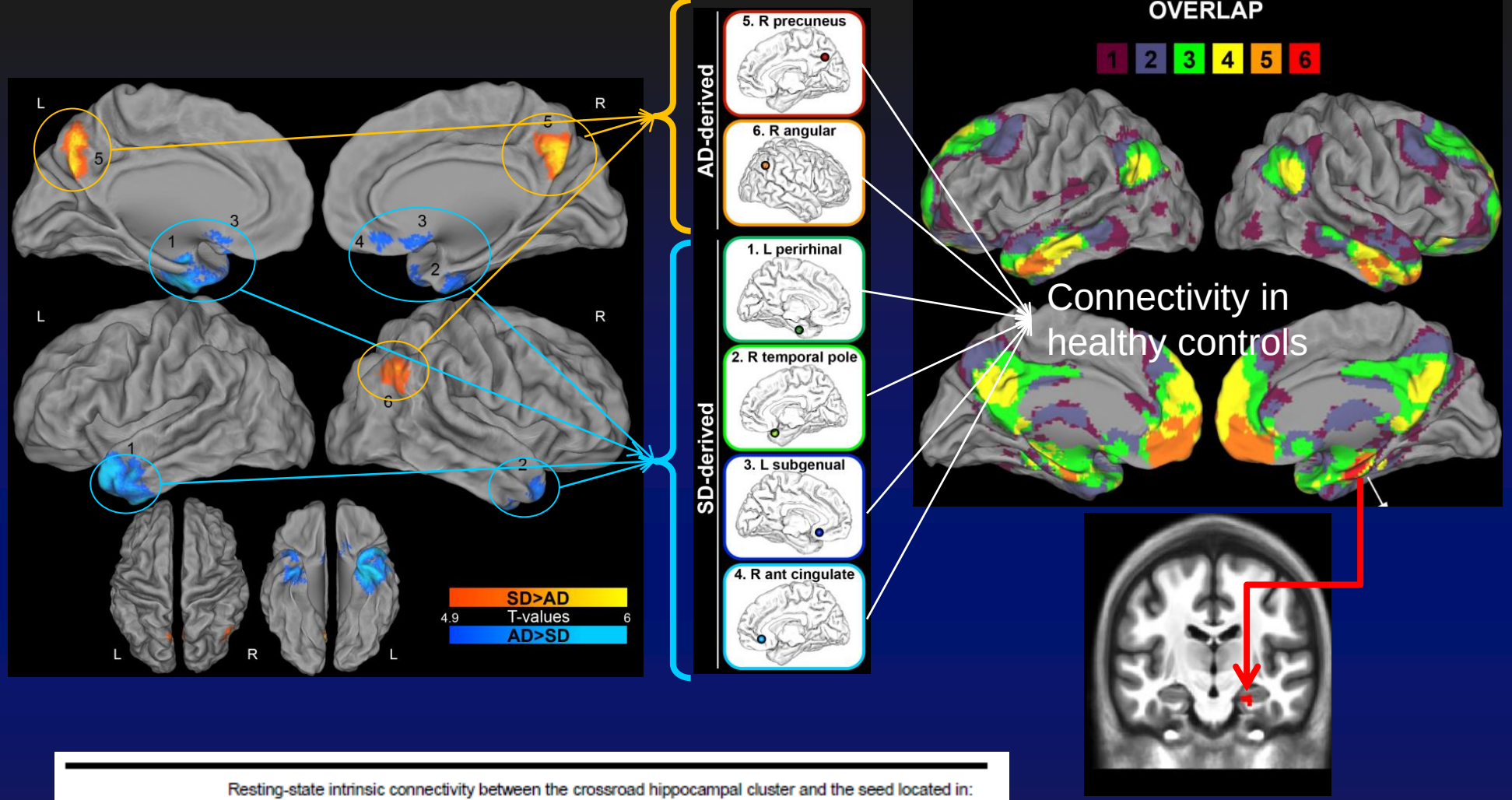


La Joie et al., 2014





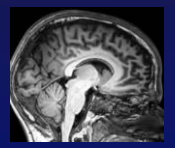
Nestor et al., 2006



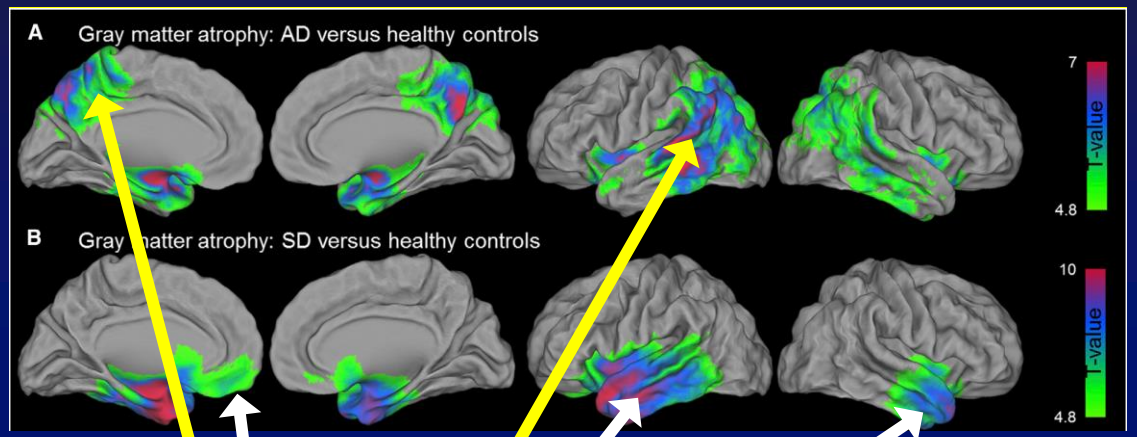
	Resting-state intrinsic connectivity between the crossroad hippocampal cluster and the seed located in:					
	L perirhinal	R temporal pole	L subgenual	R anterior cingulate	R precuneus	R angular
Episodic memory retrieval (n=56)[a]	r = -0.23 p = 0.08	r = 0.10 p = 0.46	r = -0.09 p = 0.53	r = 0.03 p = 0.84	r = 0.41 p = 0.002[b]	r = 0.35 p = 0.009
Verbal knowledge (n=54)[a]	r = -0.05 p = 0.73	r = 0.01 p = 0.94	r = -0.18 p = 0.19	r = 0.04 p = 0.80	r = -0.05 p = 0.70	r = 0.05 p = 0.70
Executive functions (n=54)[a]	r = -0.08 p = 0.56	r = 0.14 p = 0.32	r = -0.00 p = 0.98	r = 0.03 p = 0.84	r = 0.23 p = 0.10	r = 0.10 p = 0.49
Processing speed (n=55)[a]	r = 0.19 p = 0.17	r = -0.23 p = 0.10	r = -0.06 p = 0.66	r = -0.18 p = 0.18	r = - 0.11 p = 0.40	r = -0.05 p = 0.72

La Joie et al., Neuron, 2014

ATROPHY

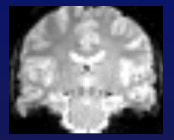


Structural MRI T1

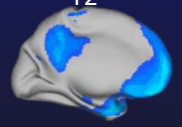


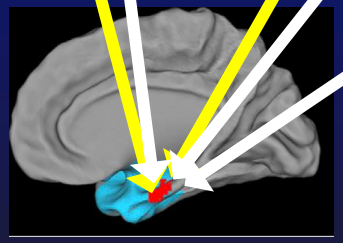
Paradox in semantic dementia: Hippocampal atrophy (comparable to AD) but (relative) preservation of episodic memory

CONNECTIVITY / NETWORKS



RS functional MRI T2*

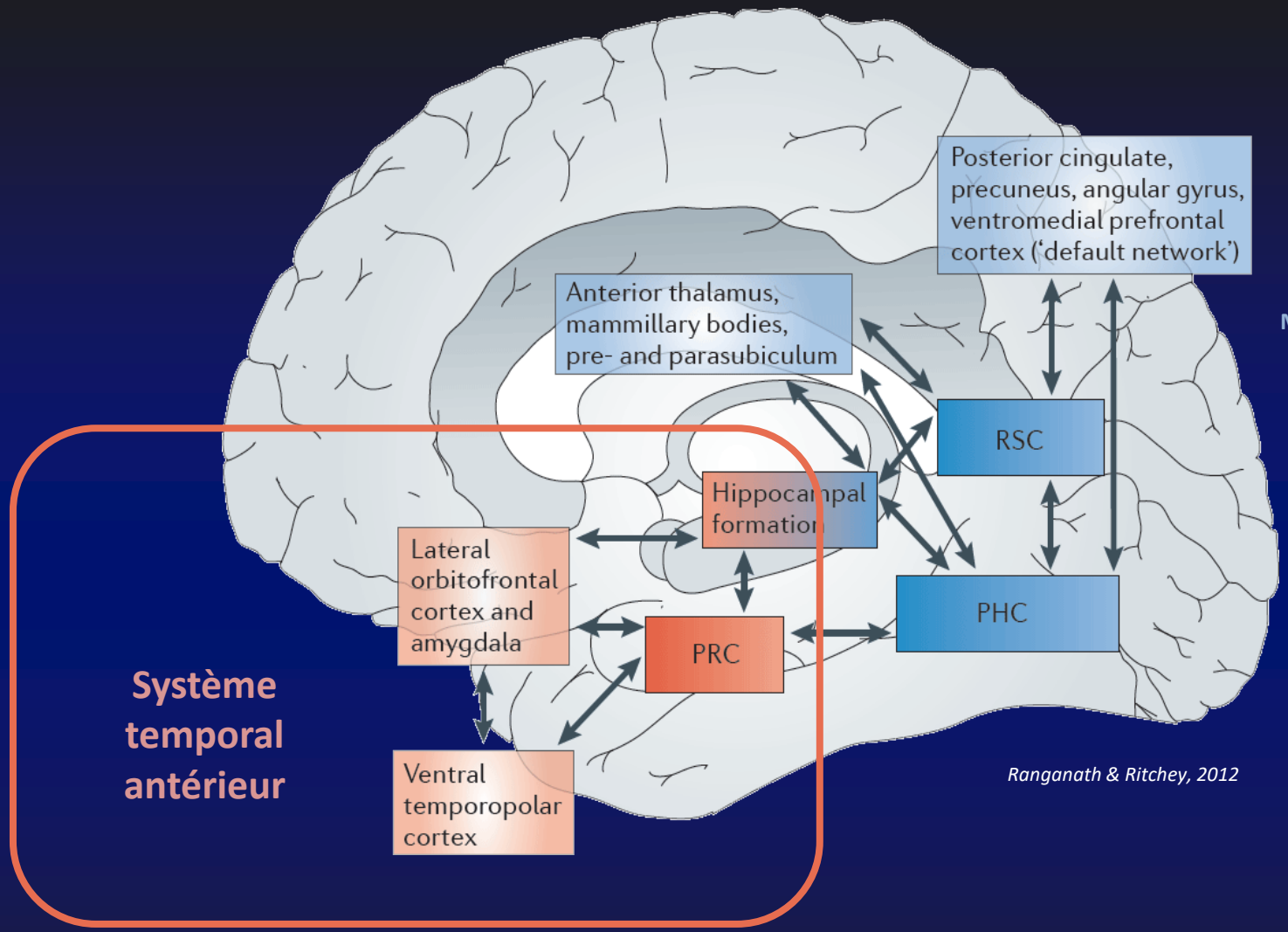




Strongly involved in episodic memory

NOT involved in episodic memory

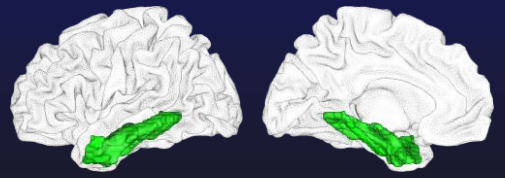
La Joie et al., Neuron, 2014

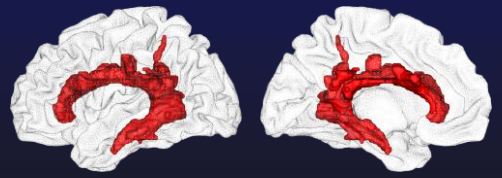


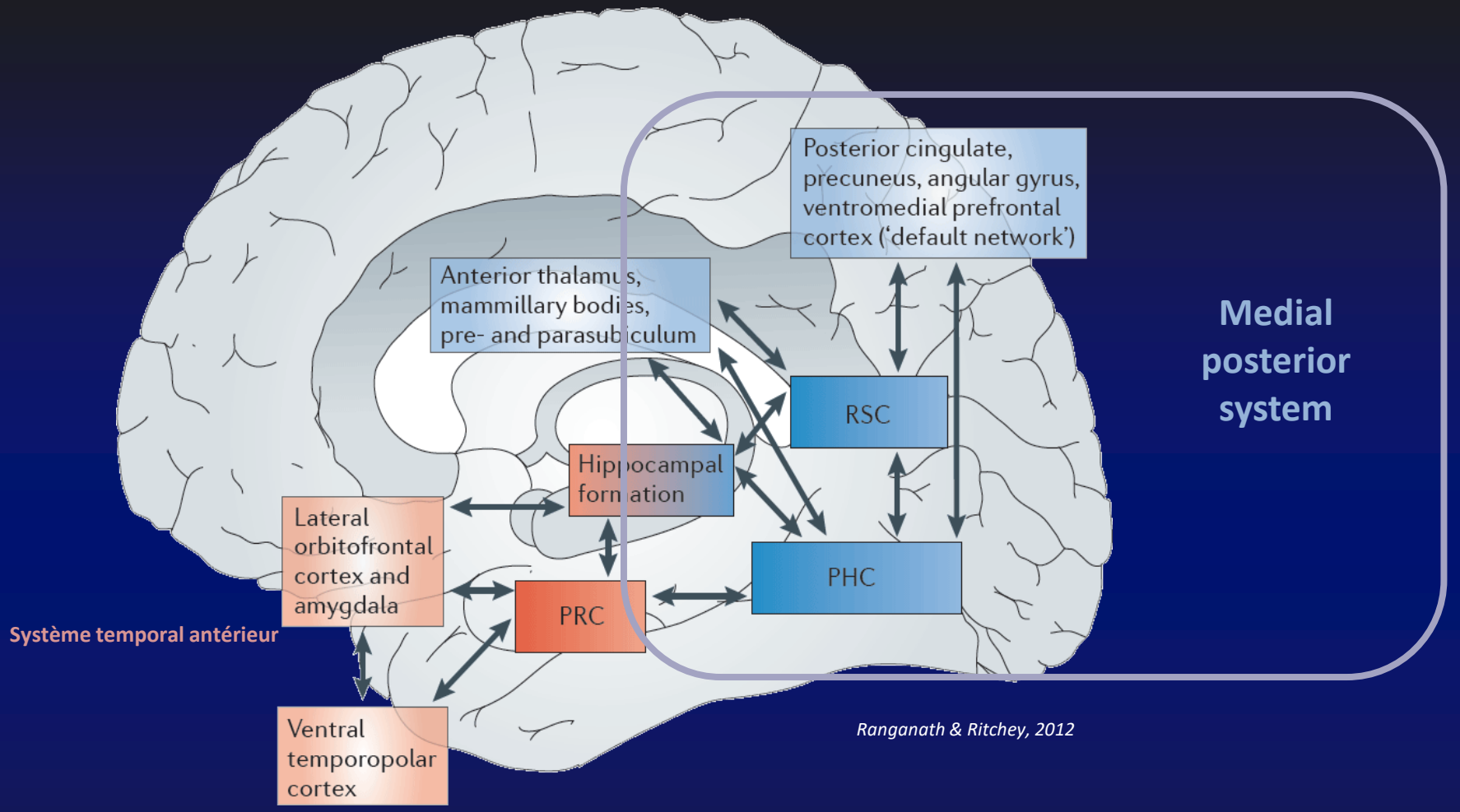
Système temporal antérieur

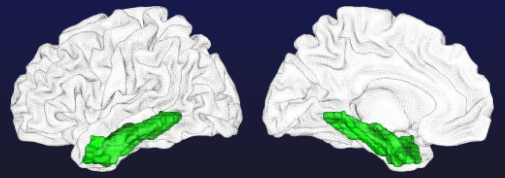
Medial posterior system

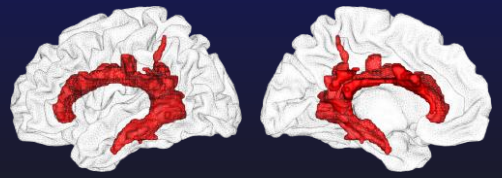
Ranganath & Ritchey, 2012



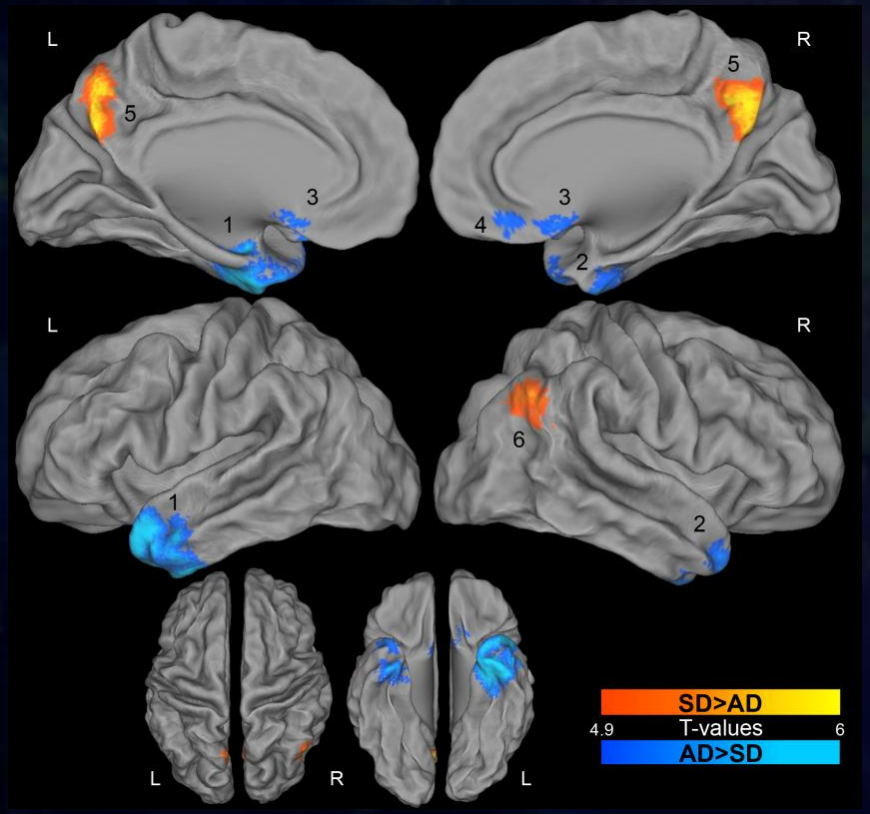



Posterior cingulate, precuneus, angular gyrus, ventromedial prefrontal cortex ('default network')
Anterior thalamus, mammillary bodies, pre- and parasubiculum
RSC
Hippocampal formation
Lateral orbitofrontal cortex and amygdala
PRC
PHC
Ventral temporopolar cortex
Système temporal antérieur
Medial posterior system
Ranganath & Ritchey, 2012

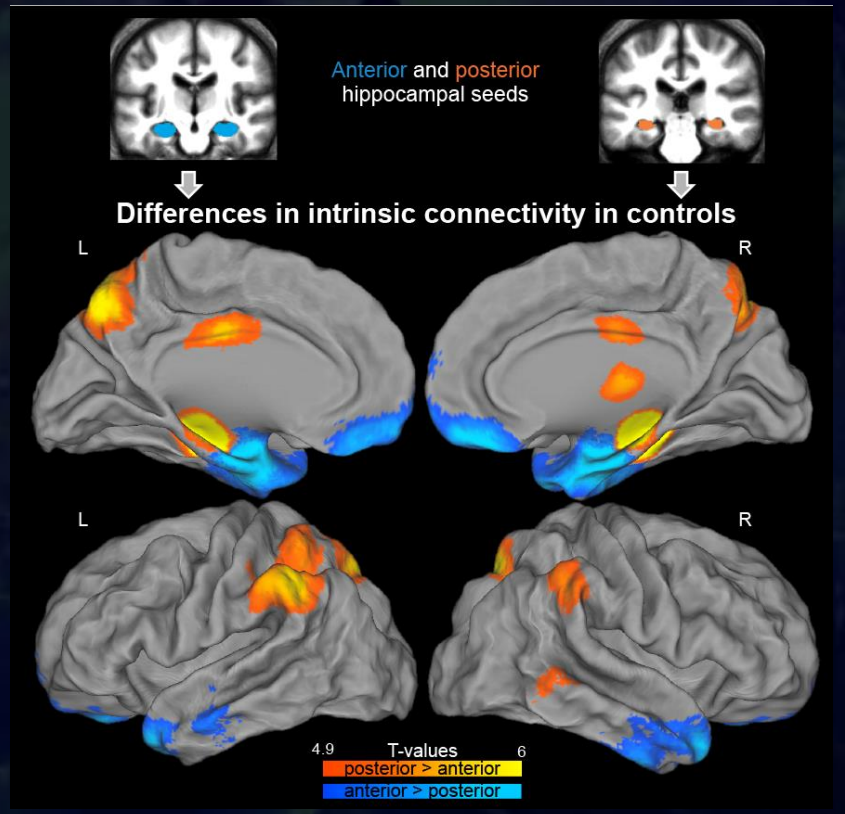




Brain regions specifically (more) altered in AD versus in SD

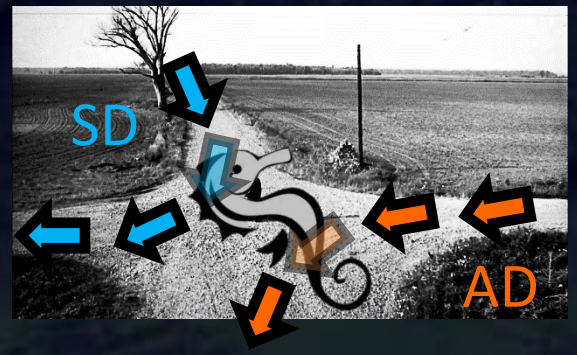


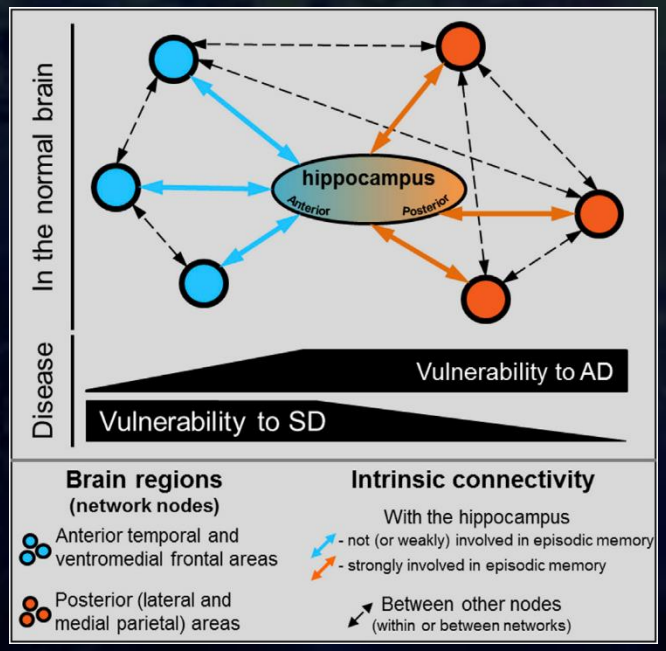
Brain regions specifically (more) connected to the posterior versus the anterior Hippocampus



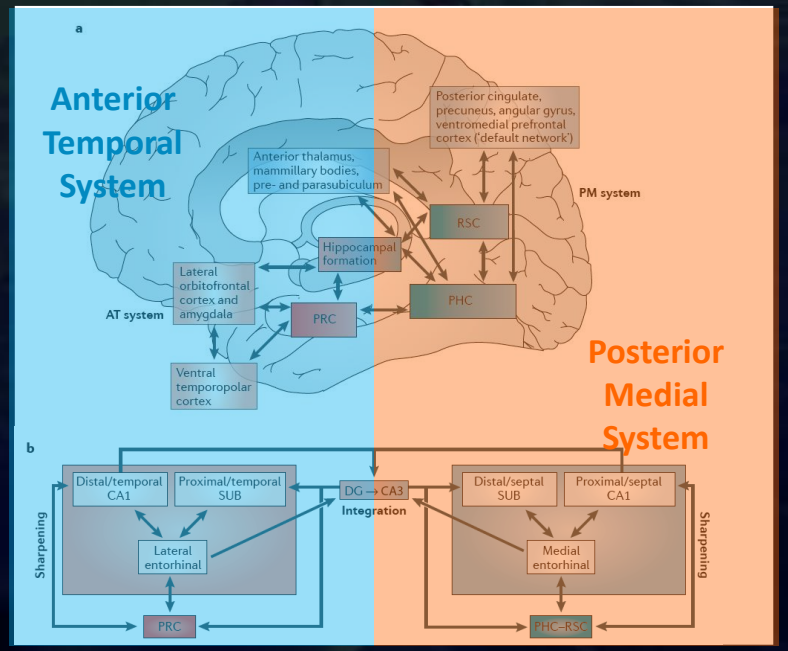
La Joie (…) Chételat, Neuron, 2014

Crossroad of dementia



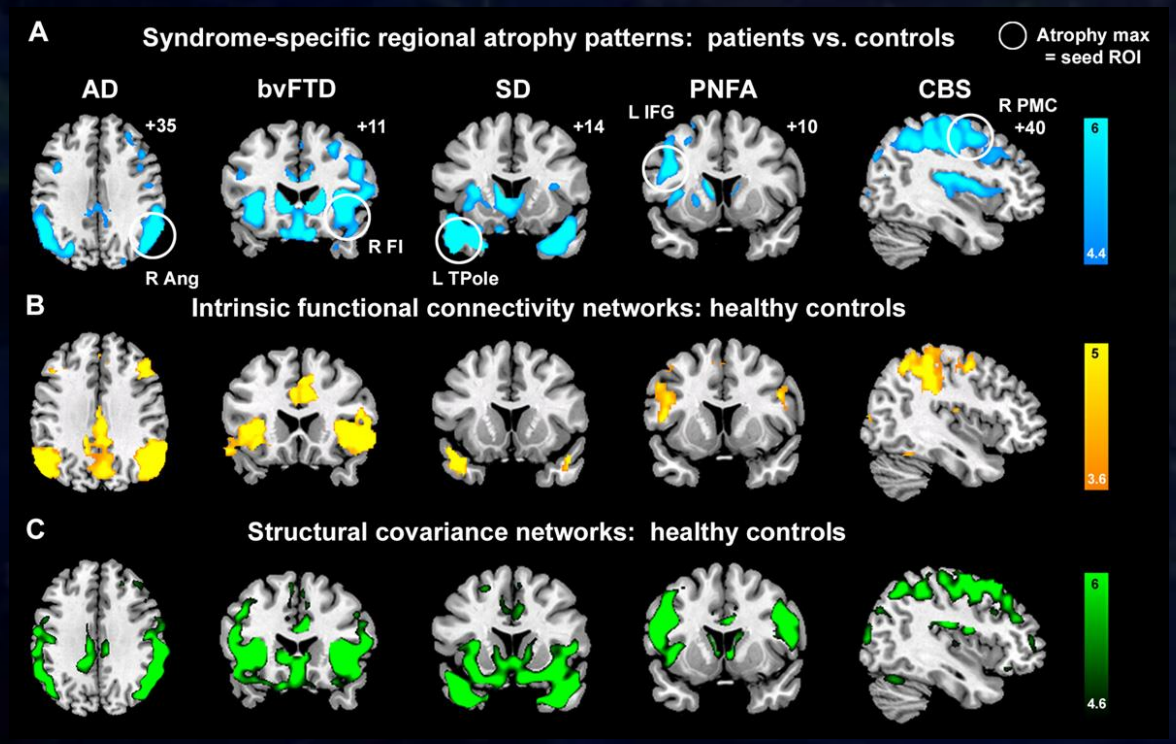


La Joie (…) Chételat, Neuron, 2014

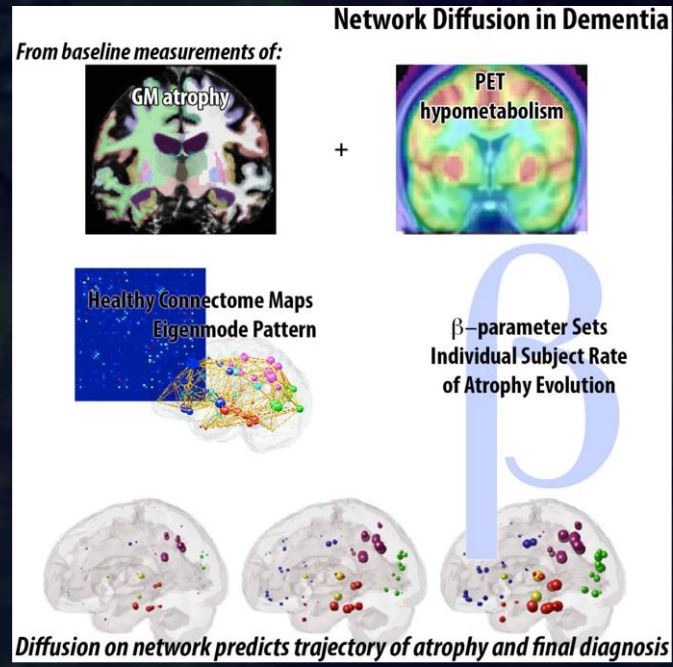


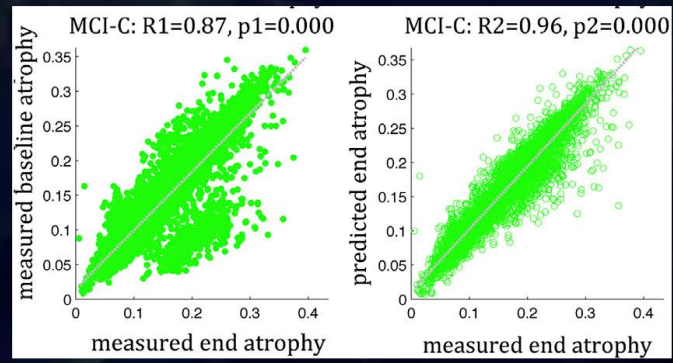
Ranganath & Ritchey, Nat Rev Neurosci 2012

The network degeneration hypothesis and network diffusion model



Seeley et al., Neuron, 2009





Raj et al., Neuron, 2012; Cell Reports 2014

Charles Duyckaerts

Alzheimer's Disease and Neuroanatomy: Hypothesis and Proposals

C. Duyckaerts, P. Delaère, and *J.-J. Hauw*

F. Boller et al. (Eds.)
Heterogeneity of Alzheimer's Disease
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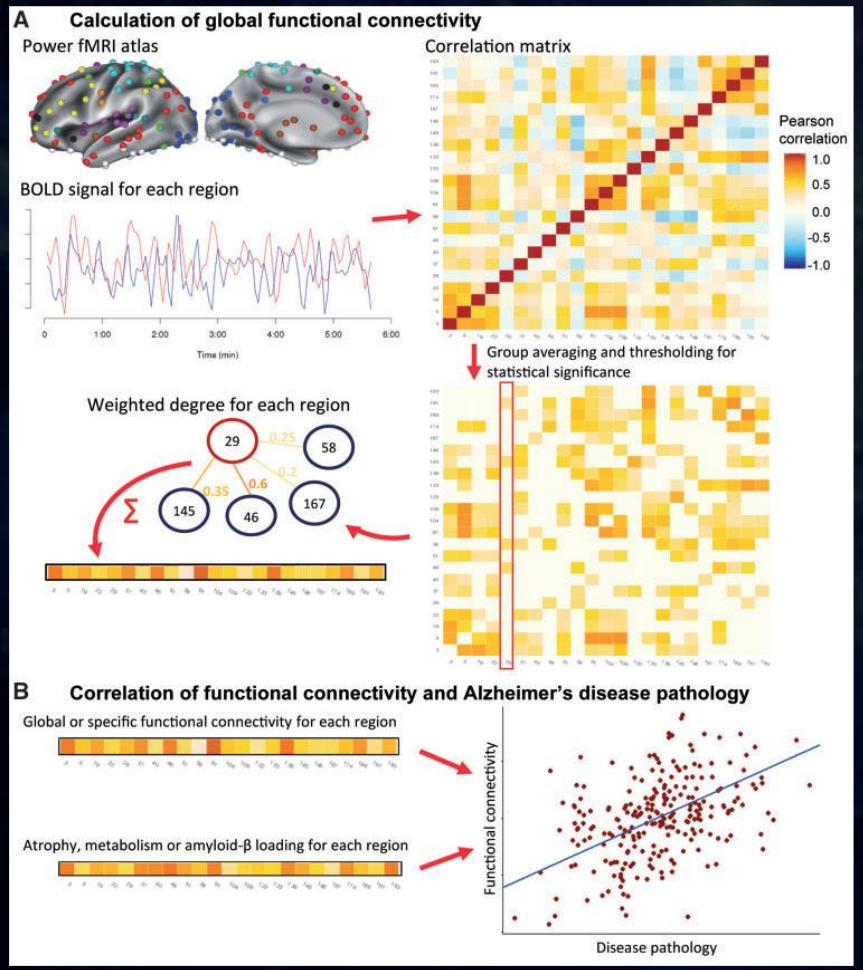
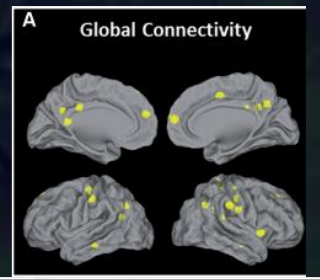
"A network of lesions

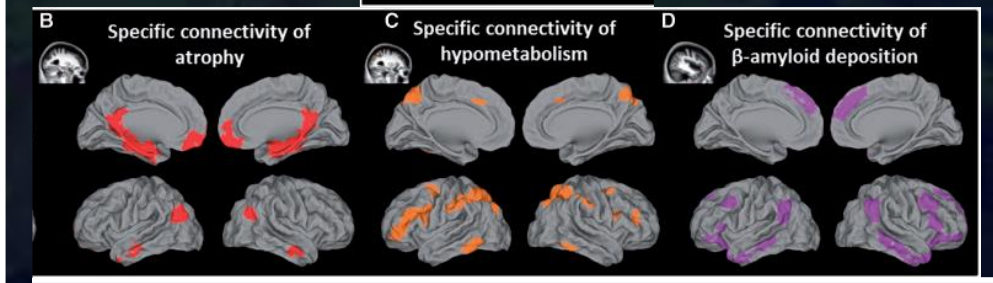
If plaques and tangle-bearing neurons are connected, then the lesions involve a network that covers the cortex"

"We found that the hippocampal stage could already demonstrate a marked involvement in cases where the neocortex was still devoid of any βA4 deposits. This suggests that the hippocampal pathology precedes the neocortical lesions and strengthens the assumption that Alzheimer's disease starts in the limbic system. On the other hand, the entorhinal prominence of the lesions could be due to the convergence of the cortico-cortical pathways on the limbic systems. By following the anatomical paths, as here hypothesized, lesions would be concentrated in the limbic system."

More than global connectivity strength, taupography actually depends on the epicenter specific connectivity







	Multiple regressions	
	Global connectivity	Specific connectivity
Baseline atrophy	$P = 0.006$	$P = 0.003$
Atrophy propagation	NS	$P < 0.0001$ b = 0.255
Baseline hypometabolism	$P = 0.0001$ b = 0.245	$P = 0.0014$ b = 0.205
Hypometabolism propagation	$P = 0.0003$ b = 0.236	NS
Baseline amyloid-β deposition	$P = 0.0028$ b = 0.175	$P < 0.0001$ b = 0.413
Amyloid-β propagation	NS	NS

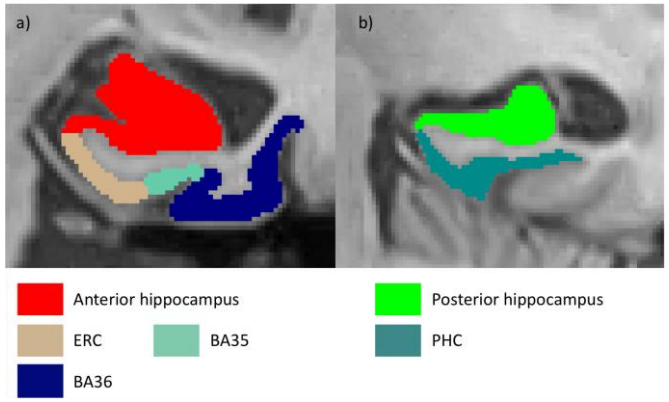
Mutlu (…) Chételat, Brain 2017

Contribution of mixed pathology to medial temporal lobe atrophy in Alzheimer's disease

- 92 patients with AD pathology at autopsy

Antemortem MRI

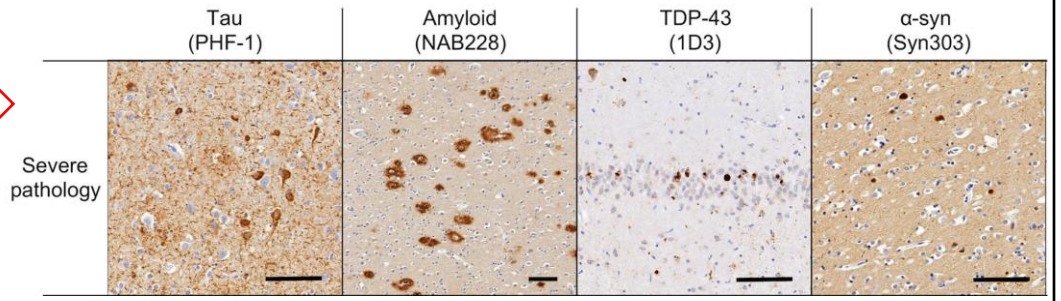
T1w – ASHS



Correlation

Neuropathological assessment

Semiquantitative scores



	Anterior hippocampus (n=89)	Posterior hippocampus (n=89)	ERC (n=76)	BA35 (n=79)	BA36 (n=79)	PHC (n=83)
One model / proteinopathy						
NFT	rho = -0.11 p = 0.14	*rho = -0.24* *p = 0.01*	rho = -4.20e-03 p = 0.49	rho = -0.15 p = 0.09	rho = -0.02 p = 0.45	rho = -0.06 p = 0.29
β-amyloid	rho = -0.09 p = 0.22	rho = -0.10 p = 0.19	rho = 0.06 p = 0.31	rho = -1.20e-03 p = 0.50	rho = 0.02 p = 0.44	rho = -0.11 p = 0.18
TDP-43	**rho = -0.46** **p = 4.17e-06**	*rho = -0.21* *p = 0.03*	*rho = -0.24* *p = 0.02*	rho = 0.03 p = 0.40	rho = 0.12 p = 0.15	rho = 0.01 p = 0.46
α-synuclein	rho = -0.04 p = 0.34	rho = 0.08 p = 0.23	rho = -0.05 p = 0.35	rho = 0.02 p = 0.43	rho = -0.15 p = 0.09	rho = -0.06 p = 0.31

De Flores et al., under review

Relevance of the cellular specificity

Charles Duyckaerts

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C. Duyckaerts, P. Delaère, and *J.-J. Hauw*

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Regional topography is not enough to explain the specificity of the clinical signs and propagation of the disease (i.e. preservation of sensori-motor networks and functions)

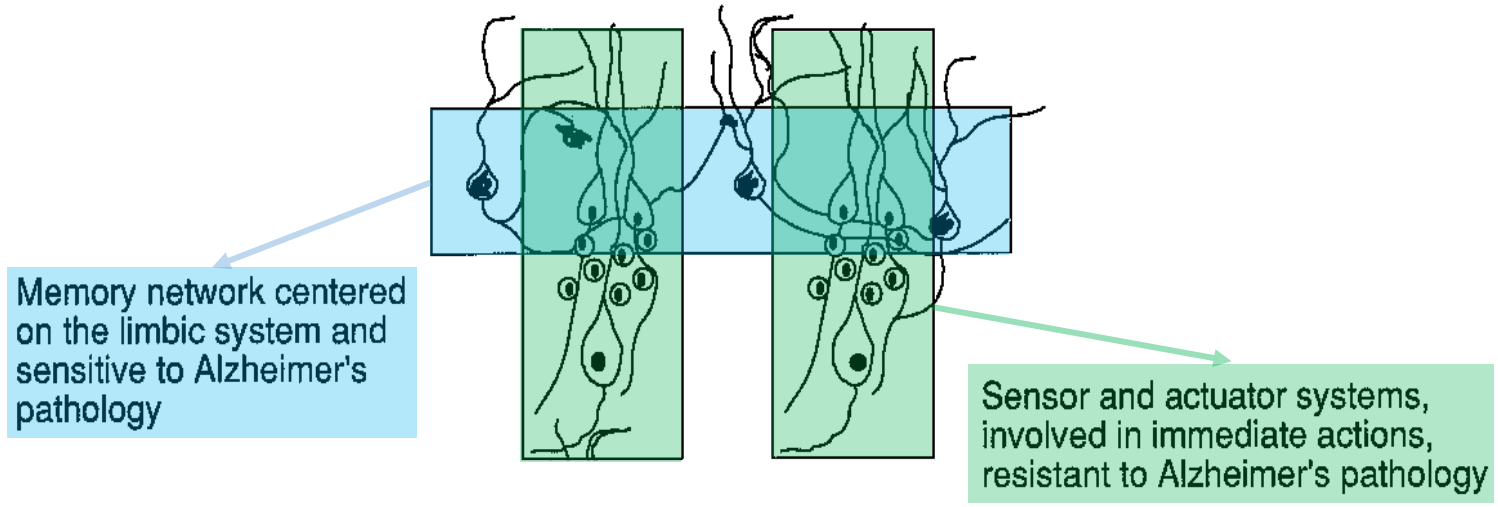
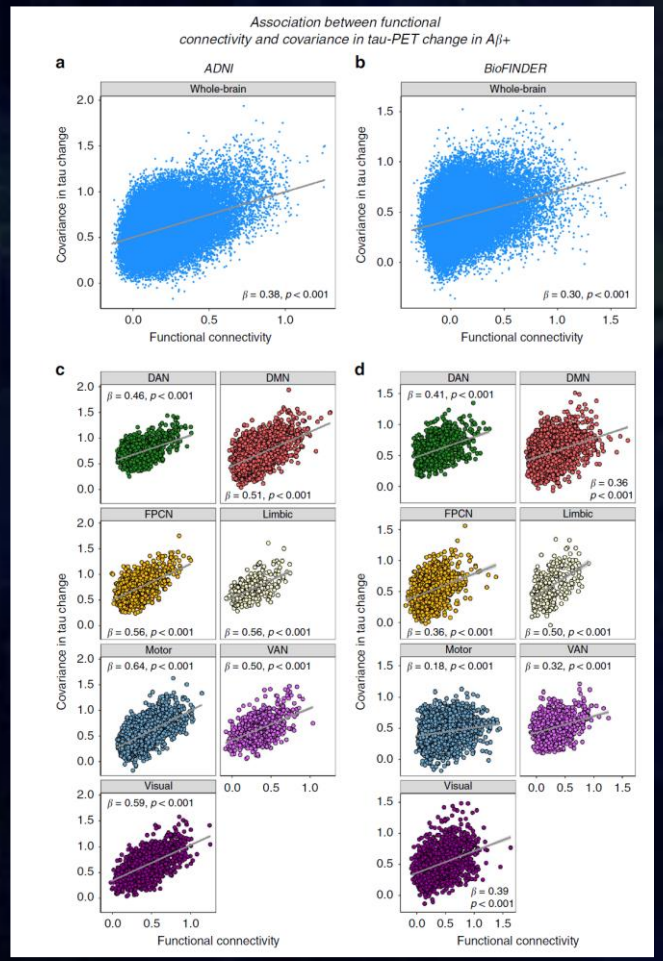


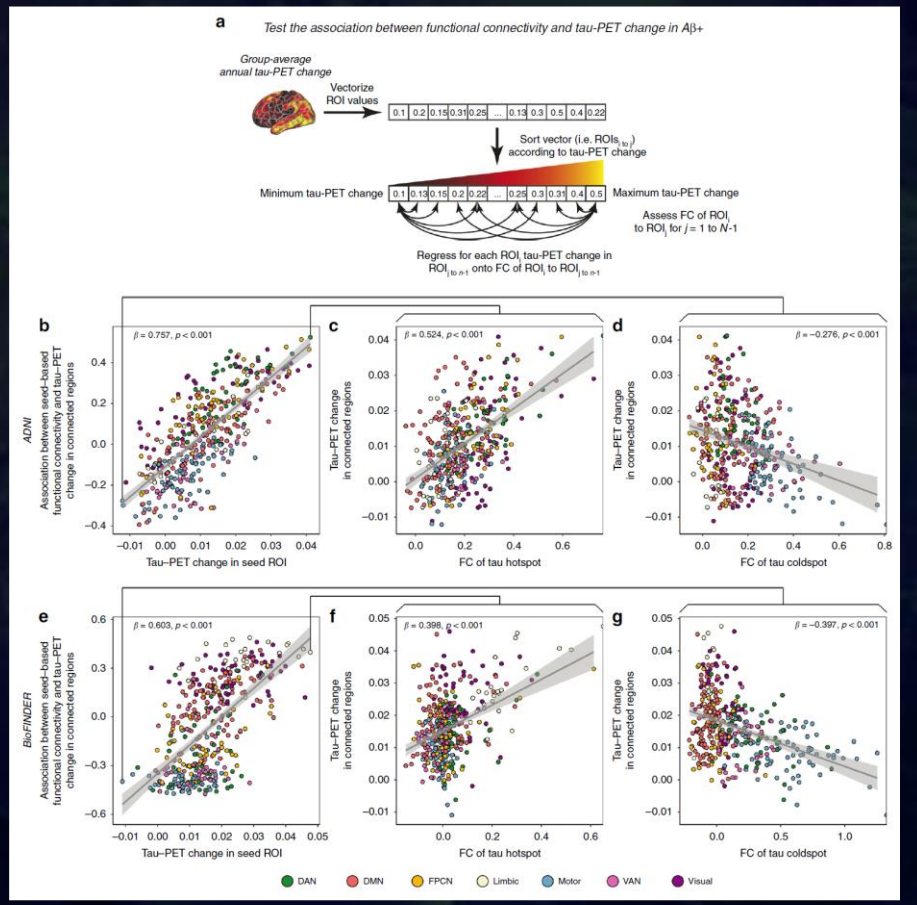
Fig. 6a–c. Dissection of brain functions by Alzheimer's pathology.

Longitudinal tau (links with Bsl fMRI connectivity)

Functionally connected regions show covariation in tau change

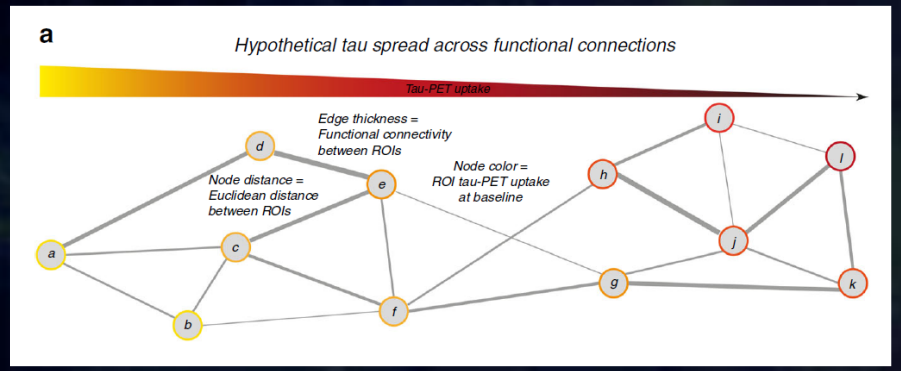


Higher connectivity with **tau hotspot** (fast tau accumulation) is associated with **faster tau accumulation in connected regions**. In contrast, **higher connectivity** with **tau coldspot** is associated with **slower tau accumulation** in connected regions.



Franzmeier et al., Nat Commun 2020

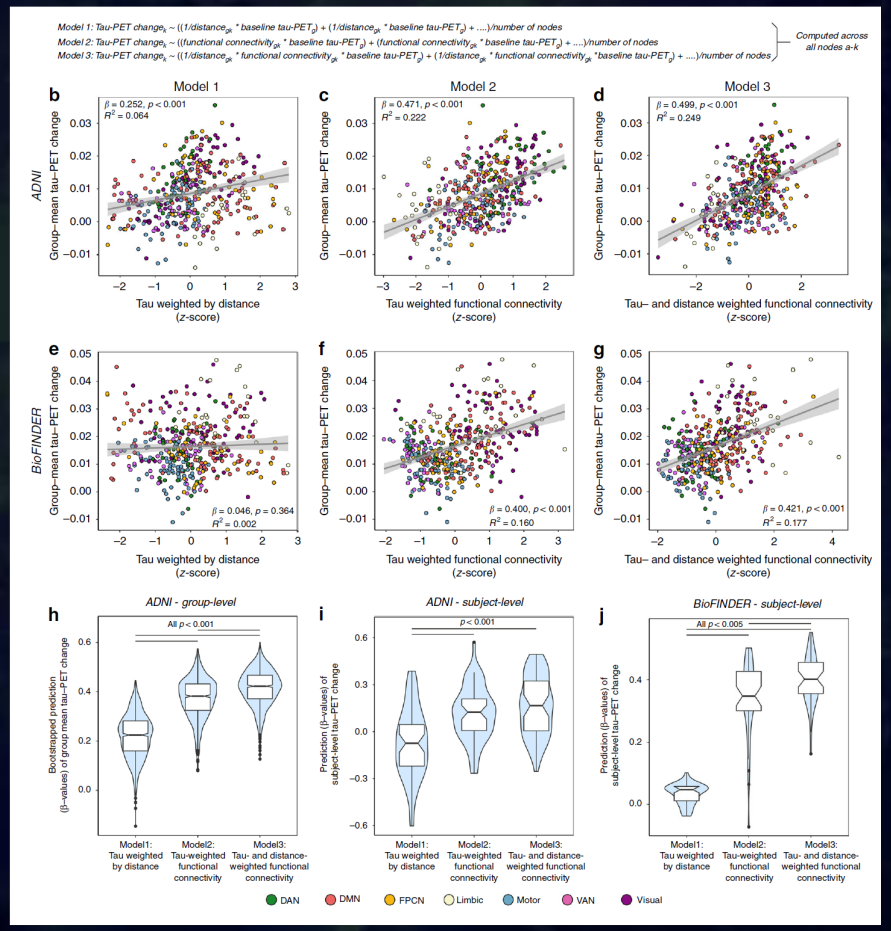
Longitudinal tau (links with Bsl fMRI connectivity)



Future tau accumulation in AD could be modeled by a combination of **baseline tau levels**, **functional connectivity**, and **distance between brain regions**.

Tau spreading is assumed to be an **active process along connected brain regions rather than passive diffusion**

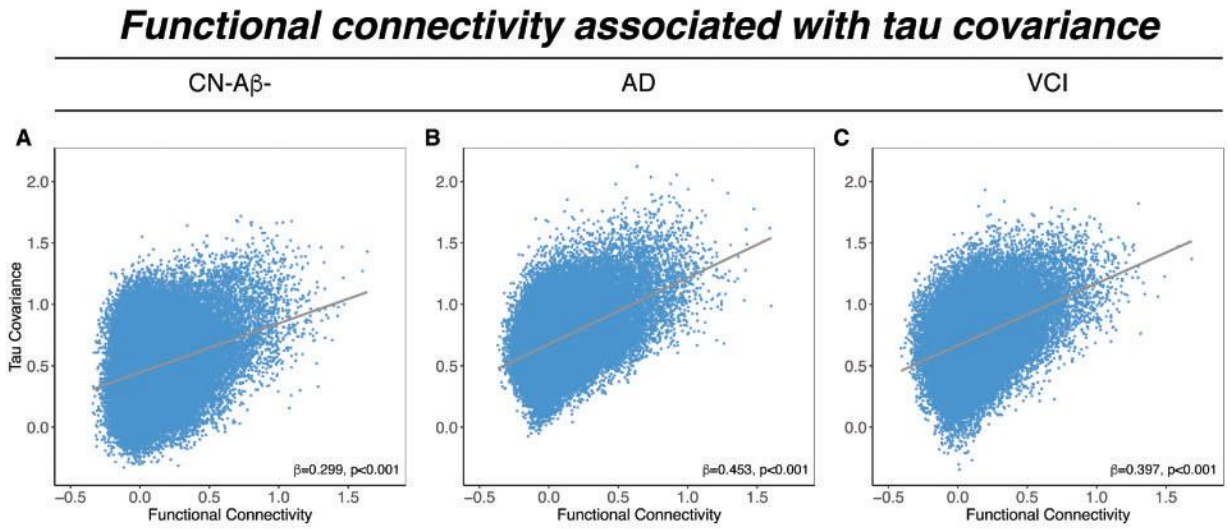
Tau **spreads throughout brain networks**, where functionally **strong and spatially short** connections increase the likelihood of tau seeding and spread.

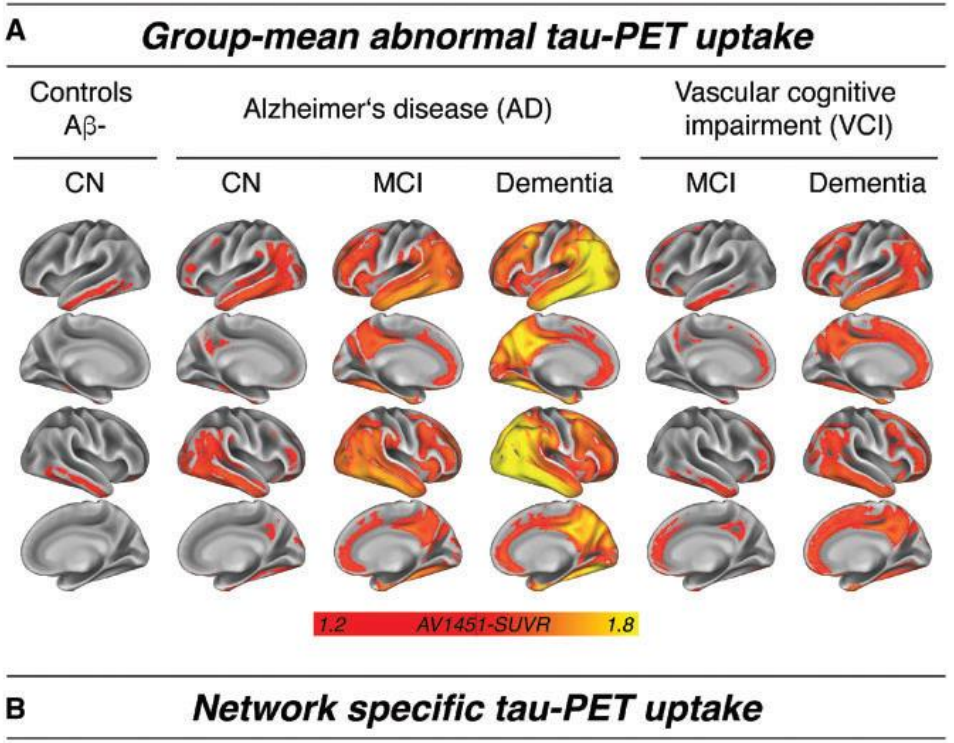


Franzmeier et al., Nat Commun 2020

Role of Ab in Tau propagation?

This spreading process / network specificity is not dependent on the presence of Aβ



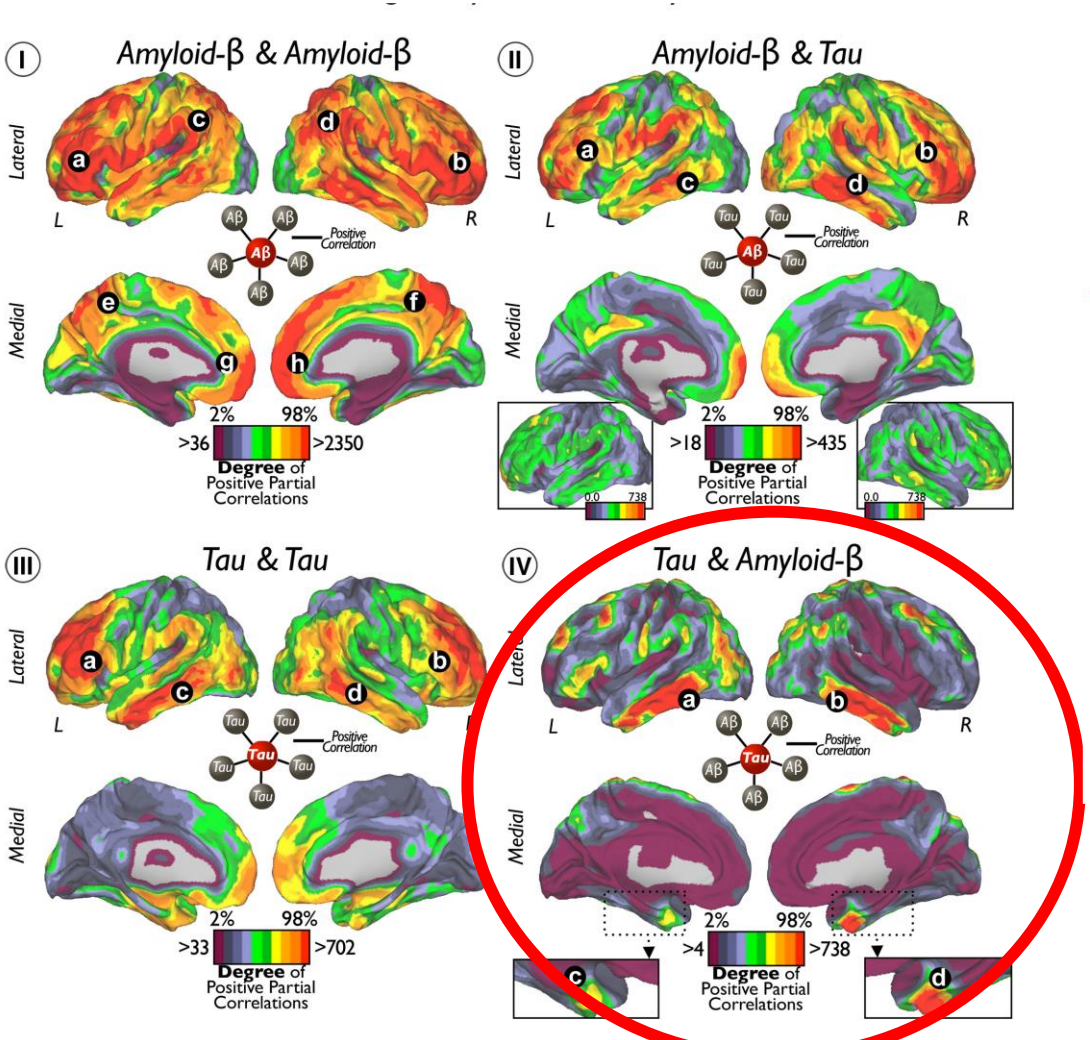


These associations between functional connectivity and tau-PET uptake were detected **regardless of presence of dementia symptoms** (mild cognitive impairment or dementia), **amyloid deposition** (as assessed by amyloid-PET) or **small vessel disease**.

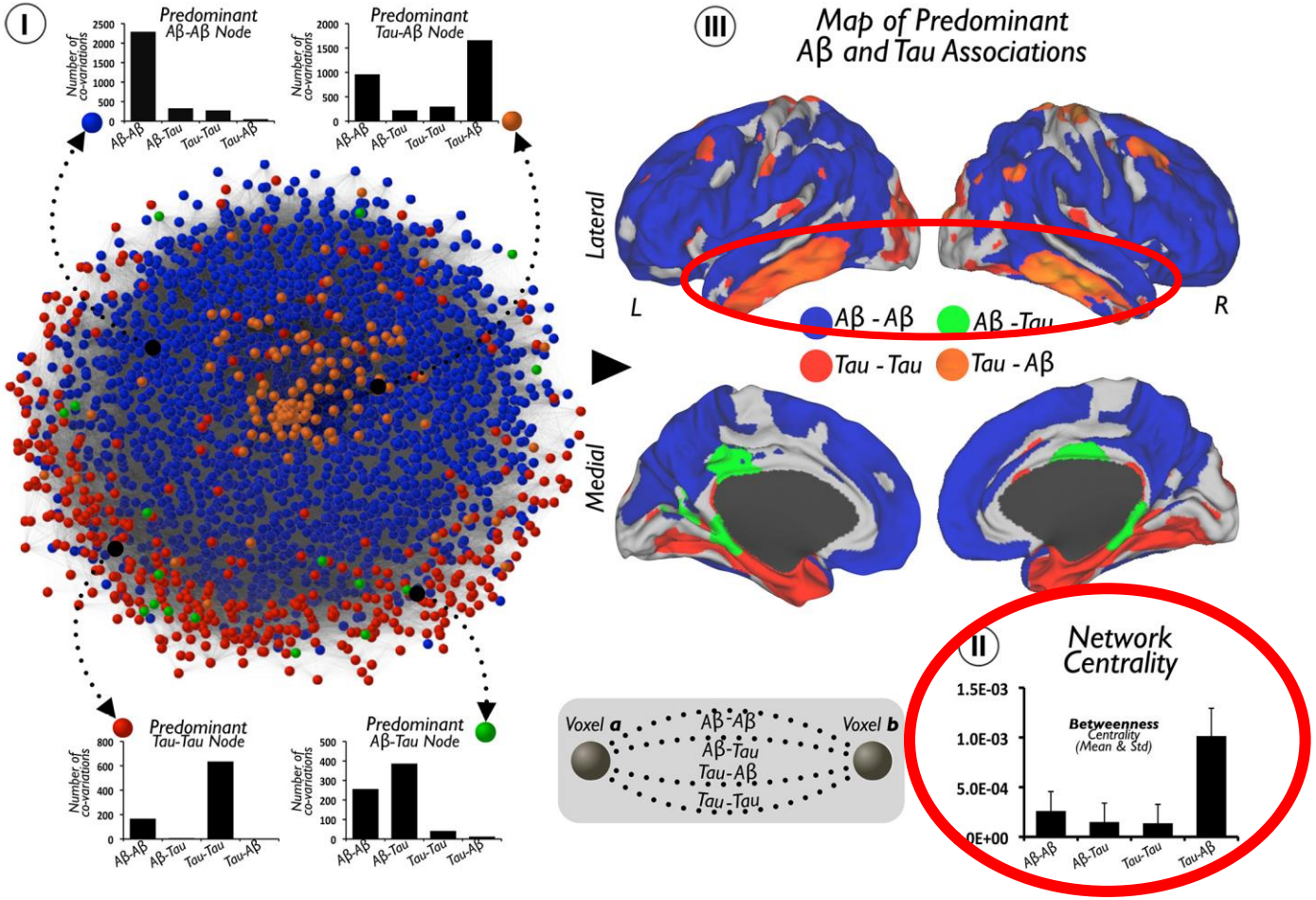
Franzmeier et al., Brain 2019

But the presence of Aβ might have an impact globally (independent from Aβ location) on the degree of tau accumulation especially in the inferior temporal lobe

Partial local-to-local and local-to-distributed within and between-modalities correlations



Hubs of **Tau** and **Amyloid-β** Network Interactions in Cognitively Normal Elderly



Tau accumulation in inferior–lateral temporal areas and entorhinal cortex that relates to massive *Aβ* elsewhere in the brain.

Sepulcre et al., J Neurosci 2016

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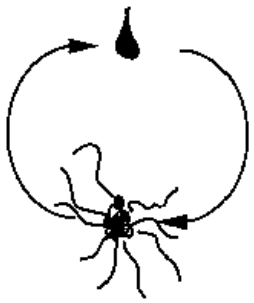
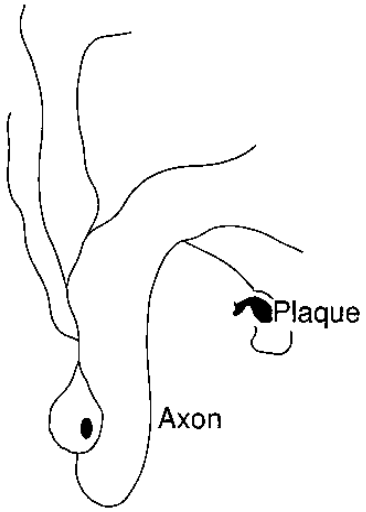


Tangles make plaques that make tangles

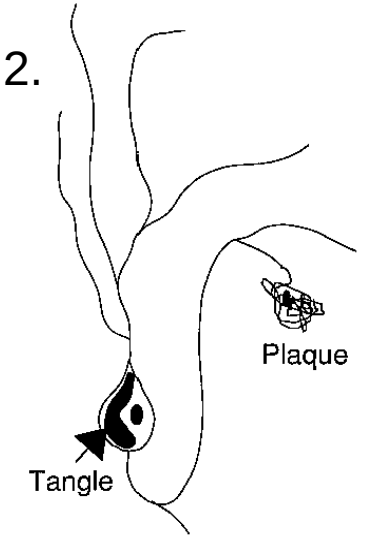
Hypothesis 2
("plaques make tangles that make plaques")

1.



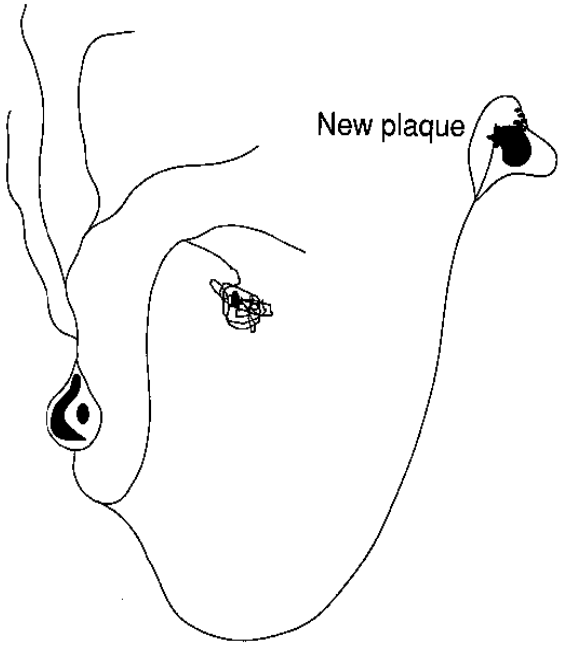
1. A plaque attracts an axon

2.



2. The neuron having axonal connection with the plaque develop tangles in its perikaryon

3.



3. The terminal part of the axon of the tangle-bearing neuron would be at the origin of a new plaque

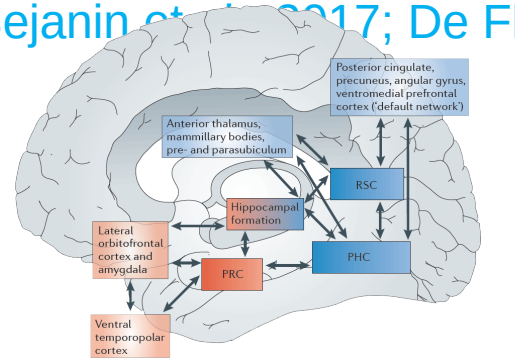
Take-home messages

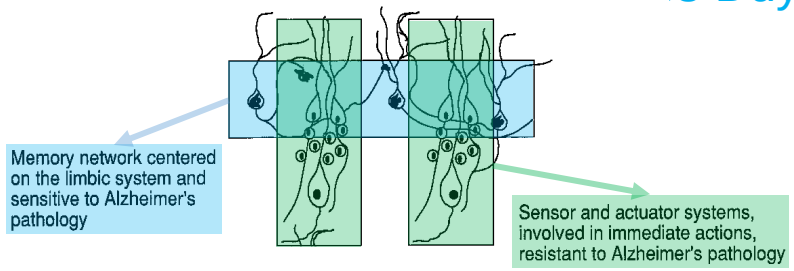
- Tau pathology spreads within brain networks mainly affecting brain hubs = nodes with high weighted degree (global connectivity) consistent with the network degeneration hypothesis and network diffusion model (Raj et al., 2014; Yang et al., 2019)

- However, brain connectivity is not enough to predict tau spreading: the epicenter (= where the pathology starts) is also relevant (specific connectivity of Multu et al. 2017, and contribution of both baseline tau topography and brain connectivity in Franzmeier et al., 2020)

- Aβ has only limited influence on this characteristic spreading, promoting/ accelerating the process with maximum interactions in the inferior temporal lobe (Franzmeier et al., 2019; Sepulcre et al., 2016)

- The spatial and even microstructural (cellular) specificity of where the pathology starts is relevant (Bejanin et al., 2017; De Flores et al; neuropathologists e.g. Charles Duyckaerts)





TAKE HOME MESSAGES

- The hippocampal region is the earliest region to be atrophied in AD with typical presentation (memory dominant)
- It is present in the prodromal and even asymptomatic stages
- Then it extends to the temporal neocortex, and cingulate, parietal and frontal brain regions → Atrophy topography in AD follows the sequence of NFT in AD
- Hippocampal atrophy can be assessed visually (e.g. using visual scales), with region-of-interest approaches (automatic techniques have been developped) and using automatic whole-brain (voxelwise or cortical thickness) techniques
- Hippocampal atrophy is useful to support the diagnosis of AD, but is not specific to AD
- (hippocampal) atrophy is useful to monitor the progression of the disease (it progresses as the disease and cognitive impairment progress)
- Hippocampal subfield volumetry may allow to increase specificity as the CA1 subfield seems to be more specifically involved (in early stages) → in development
- Hippocampal atrophy has distant functional effects and the specific hippocampal region to be altered is important as it would have distinct clinical/cognitive implications due to the differential connectivity across the hippocampus

DEMENCE – Définition – DSM5

La démence = *trouble neurocognitif majeur* dans le DSM-5: déclin cognitif qui compromet l'indépendance de la personne.
Les symptômes varient selon les types de démence dont le plus fréquent est la maladie d'Alzheimer.

Critères diagnostiques de la démence du *DSM-5**

1.Évidence d'un déclin cognitif significatif par rapport au niveau de performance antérieur dans un domaine cognitif ou plus (attention complexe, fonctions exécutives, apprentissage et mémoire, langage, perception-motricité ou cognition sociale) sur la base :

1. d'une préoccupation de l'individu, d'un informateur bien informé, ou du clinicien quant à un déclin significatif de la fonction cognitive ; et
2. d'un déficit de la performance cognitive, de préférence documenté par des tests neuropsychologiques standardisés ou, en leur absence, une autre évaluation clinique quantifiée.

2.Les déficits cognitifs interfèrent avec l'indépendance dans les activités quotidiennes (c.-à-d., au minimum, besoin d'aide pour les activités instrumentales complexes de la vie quotidienne telles que le paiement des factures ou la gestion des médicaments).

3.Les déficits cognitifs ne se produisent pas exclusivement dans le cadre d'un délirium.

4.Les déficits cognitifs ne sont pas mieux expliqués par un autre trouble mental (par exemple, le trouble dépressif majeur, la schizophrénie).

(*) DSM-5, Manuel diagnostique et statistique des troubles mentaux ("*Diagnostic and Statistical Manual of Mental Disorders*"), publié par l'*American Psychiatric Association* en 2013.

Spécificateurs

Sous-types de démence selon la cause

•maladie d'Alzheimer
•dégénérescence lobaire fronto-temporale (démence frontotemporale)
•maladie avec corps de Lewy (démence à corps de Lewy)
•maladie vasculaire (démence vasculaire)
•lésion cérébrale traumatique
•substance ou un médicament
•infection au HIV
•maladie à prion
•maladie de Parkinson
•maladie de Huntington
•autre condition médicale
•multiples étiologies (causes)
•non spécifié.

Comportements

Sans perturbation du comportement
Si la perturbation cognitive n'est pas accompagnée d'une perturbation du comportement cliniquement significative.

Avec perturbation du comportement
Si la perturbation cognitive est accompagnée d'une perturbation cliniquement significative du comportement (par exemple, symptômes psychotiques, perturbation de l'humeur, agitation, apathie, ou d'autres symptômes comportementaux).

Les **symptômes psychotiques** sont courants, en particulier au stade léger à modéré du trouble dû à la maladie d'Alzheimer, à la maladie à corps de Lewy et à la dégénérescence lobaire fronto-temporale. La paranoïa et d'autres délires sont fréquents et souvent un thème de persécution peut être un aspect important de l'idéation délirante. Les hallucinations, notamment visuelle mais impliquant aussi d'autres modalités, peuvent survenir.

Sévérité

•**Légère** : difficultés avec les activités instrumentales de la vie quotidienne (par exemple, les travaux ménagers, la gestion de l'argent).
•**Modérée** : difficultés avec les activités de base de la vie quotidienne (par exemple, l'alimentation, l'habillage).
•**Sévère** : complètement dépendant.